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DESCRIPTION

ALKYNYLPURINE COMPOUNDS AND PRODUCTION METHODS THEREOF

Technical Field

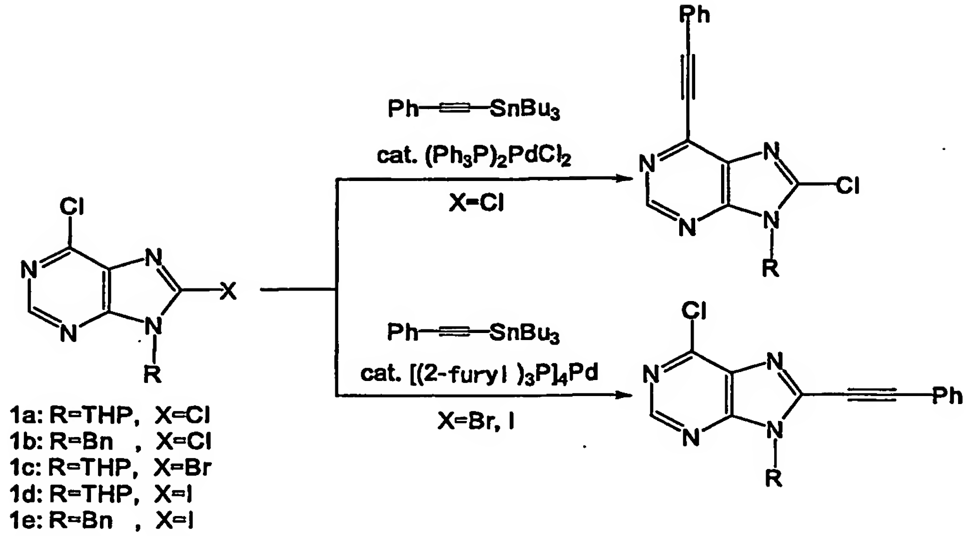
The present invention relates to an alkynylpurine compound (particularly, an alkynylpurine compound having an alkynyl moiety at the 2-, 6- or 8-position of its purine nucleus), which is a key intermediate for the production of medicaments, a salt thereof and a production method thereof.

Background Art

Alkynylpurine compound is a key intermediate for the production of medicaments such as ischemia-reperfusion injury inhibitors (JP-A-2001-64183), therapeutic agents of diabetes (WO99/35147), therapeutic agents of tuberculosis (A.K. Bakkestuen et al., Bioorg. Med. Chem. Lett., 10 (2000), 1207-1210) and the like.

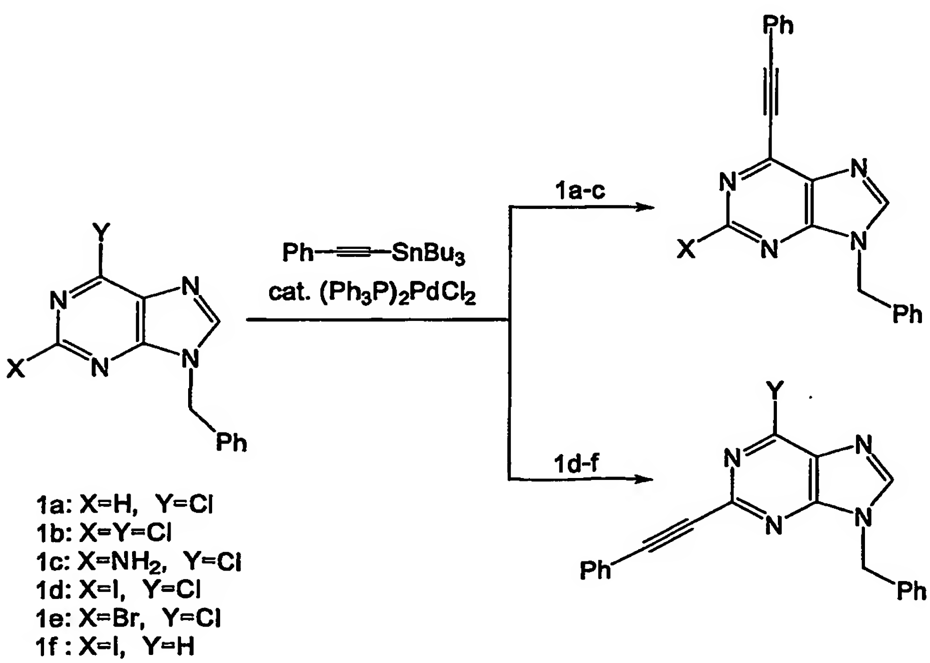
As a production method of the alkynylpurine compound, for example, the methods described in the following references (1)-(3) can be shown.

(1) According to the method described in "Regiochemistry in the Pd-Mediated Coupling between 6,8-Dihalopurines and Organometallic Reagents", Acta Chemica Scandinavica 53 (1999), 366-372 by Nolsφe et al., alkynylpurine compounds can be obtained by reacting a 6,8-dihalogenopurine compound 1a-1e with Ph-C≡C-$SnBu_3$ in the presence of bis(triphenylphosphine)palladium dichloride [i.e. $(Ph_3P)_2PdCl_2$] or tetrakis[tri(2-furyl)phosphine]palladium [i.e. $[(2\text{-furyl})_3P]_4Pd$].



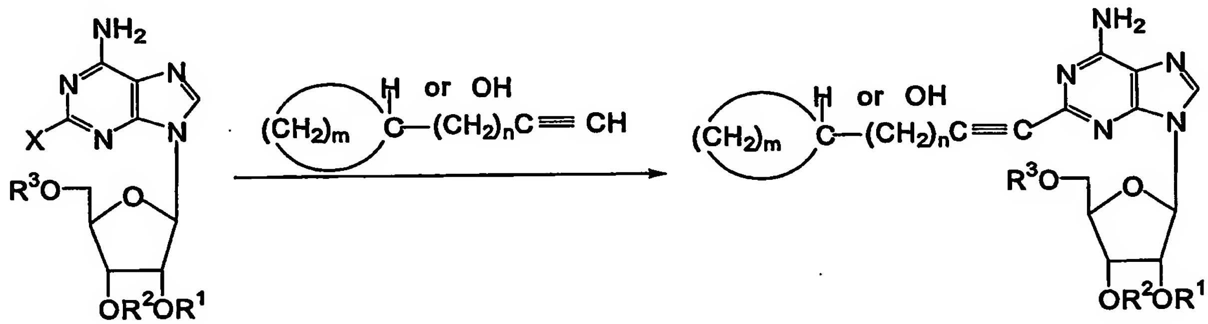
wherein THP is tetrahydropyranyl and Bn is benzyl.

(2) According to the method described in "9-Benzylpurines with Inhibitory Activity Against *Mycobacterium tuberculosis*", Bioorg. Med. Chem. Lett., 10 (2000) 1207-1210 by A.K. Bakkestuen et al., alkynylpurine compounds useful as intermediates for medicaments can be obtained by reacting a halogenopurine compound 1a-1f with Ph-C≡C-$SnBu_3$ in the presence of bis(triphenylphosphine)palladium dichloride [i.e. $(Ph_3P)_2PdCl_2$].



(3) According to the method described in EP 0488336 A1,

alkynylpurine compounds useful as medicaments can be obtained by reacting a halogenopurine compound with an alkyne compound in the presence of a palladium catalyst (e.g., bis(triphenylphosphine)palladium dichloride etc.) and a copper compound (e.g., cuprous iodide etc.) according to the following reaction scheme:



wherein R^1, R^2 and R^3 may be the same or different and each independently represent a hydrogen atom, a hydroxy-protecting group or a phosphoric acid residue, X represents bromine or iodine, m is an integer of 2 to 7 and n is 0 or an integer of 1 to 3.

The methods described in references (1) and (2) both utilize a coupling reaction (Stille reaction) between Ph-C≡C-$SnBu_3$ (alkynylating agent), which is stable as a metal acetylide, and a halogenopurine by the use of a palladium catalyst. However, the alkynylating agent has extremely high toxicity, because it is an organotin reagent, and the use of the alkynylating agent for the production of medicaments is not preferable. In addition, the methods described in references (1) and (2) are also associated with the problem that the production cost of alkynylpurine compound becomes high because the synthesis of the alkynylating agent is extremely difficult.

Moreover, the above-mentioned methods require Ph-C≡C-$SnBu_3$ in an amount of at least 1 equivalent, generally not less than 1 equivalent, relative to a halogenopurine

compound, which is a substrate, and organotin compounds, which are to be wasted after the reaction, are produced in an amount of not less than 1 equivalent. Therefore, the above-mentioned methods are not environmentally or economically superior.

In addition, inasmuch as the methods described in references (1), (2) and (3) are based on an idea that a halogenopurine compound and an alkynylating agent or alkynyl compound are coupled for each objective product, further modification of the alkynyl moiety of the alkynylpurine compound obtained according to the method described in references (1), (2) or (3) is not assumed. Therefore, the methods described in references (1), (2) and (3) are problematic in that many alkynylpurine derivatives useful as a medicament cannot be synthesized conveniently from the obtained alkynylpurine compounds, and the like.

Accordingly, the development of a method of producing an alkynylpurine compound useful as an intermediate for the production of medicaments (i.e., alkynylpurine compound whose alkynyl moiety can be easily modified, and as a result, a number of alkynylpurine derivatives can be derived) safely, conveniently and economically from the corresponding purine compound, as well as the development of an alkynyl purine compound useful as an intermediate for medicament production are desired.

Disclosure of the Invention

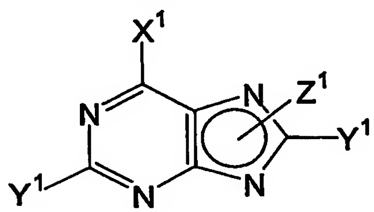
It is therefore an object of the present invention to provide a production method of an alkynylpurine compound useful as an intermediate for the production of medicaments and a salt thereof safely, conveniently and economically from the corresponding purine compound and a salt thereof, as well as an alkynylpurine compound useful as an intermediate for the production of medicaments and a salt thereof.

In view of the above-mentioned problems, the present

inventors have conducted intensive studies and, as a result, found that an ethynylpurine compound having an ethynyl group as an alkynyl moiety can be converted to various alkynylpurine compounds, as a result of which found a method that can produce a purine compound having an alkynyl moiety at the 2-, 6- or 8-position (i.e., alkynylpurine compound whose alkynyl moiety can be easily modified and can derive a number of alkynylpurine derivatives), which is a key intermediate for medicaments, safely, conveniently and economically, which resulted in the completion of the invention.

Accordingly, the present invention relates to the following [1] - [23].

[1] A compound represented by the formula (I-1):



(I-1)

wherein

X^1 is an alkyl group, an alkoxy group, an aryl group, an optionally protected amino group, a halogen atom or a hydrogen atom,

one of Y^1 is a group represented by the formula: R-C≡C-

wherein R is a hydrogen atom, a hydrocarbon group optionally having substituents, an aryl group optionally having substituents or a heterocyclic group optionally having substituents, and the other Y^1 is a hydrogen atom, and

Z^1 is an alkyl group, a sugar group, an amino-protecting group or a hydrogen atom, which is attached to a nitrogen atom at the 7- or 9-position of the purine nucleus,

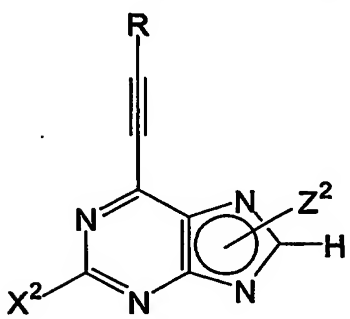
or a salt thereof.

[2] The compound of the above-mentioned [1], wherein X^1 is a halogen atom, R is a hydrogen atom or $Me_2(OH)C-$, and Z^1 is an amino-protecting group or a hydrogen atom.

[3] The compound of the above-mentioned [1] or [2], wherein X^1 is a chlorine atom.

[4] The compound of any of the above-mentioned [1] to [3], wherein Z^1 is tetrahydropyran-2-yl, benzyl or a hydrogen atom.

[5] A compound represented by the formula (I-2):



(I-2)

wherein

R is a hydrogen atom, a hydrocarbon group optionally having substituents, an aryl group optionally having substituents or a heterocyclic group optionally having substituents,

X^2 is an alkyl group, an alkoxy group, an aryl group, an optionally protected amino group, a halogen atom or a hydrogen atom, and

Z^2 is an alkyl group, a sugar group, an amino-protecting group or a hydrogen atom, which is attached to a nitrogen atom at the 7- or 9-position of the purine nucleus,

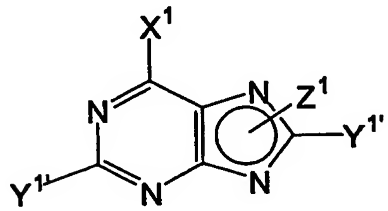
or a salt thereof.

[6] The compound of the above-mentioned [5], wherein R is a hydrogen atom or $Me_2(OH)C-$, X^2 is an optionally protected amino group, and Z^2 is an amino-protecting group or a hydrogen atom.

[7] The compound of the above-mentioned [5] or [6], wherein Z^2

is tetrahydropyran-2-yl, benzyl or a hydrogen atom.

[8] A production method of a compound represented by the formula (I-1'):



(I-1')

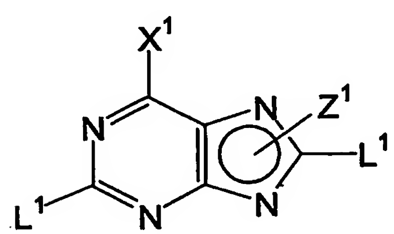
wherein

X^1 is an alkyl group, an alkoxy group, an aryl group, an optionally protected amino group, a halogen atom or a hydrogen atom,

Z^1 is an alkyl group, a sugar group, an amino-protecting group or a hydrogen atom, which is attached to a nitrogen atom at the 7- or 9-position of the purine nucleus, and

one of $Y^{1'}$ is a group represented by the formula: $Me_2(OH)C-C{\equiv}C-$, and the other $Y^{1'}$ is a hydrogen atom,

or a salt thereof, which comprises reacting a compound represented by the formula (II-1):



(II-1)

wherein

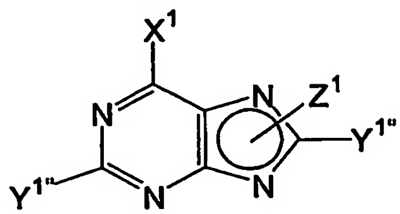
X^1 and Z^1 are as defined above, and

one of L^1 is a halogen atom, and the other L^1 is a hydrogen atom, provided that when X^1 is a halogen atom, L^1 is a halogen atom having higher leaving ability than the halogen atom represented by X^1,

or a salt thereof, with a compound represented by the formula (III): $Me_2(OH)C-C{\equiv}CH$, in the presence of a metal catalyst and a

base (1).

[9] A production method of a compound represented by the formula (I-1''):



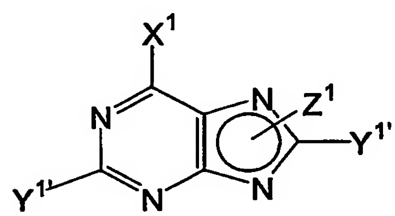
(I-1'')

wherein

X^1 is an alkyl group, an alkoxy group, an aryl group, an optionally protected amino group, a halogen atom or a hydrogen atom,

Z^1 is an alkyl group, a sugar group, an amino-protecting group or a hydrogen atom, which is attached to a nitrogen atom at the 7- or 9-position of the purine nucleus, and

one of $Y^{1''}$ is a group represented by the formula: HC≡C-, and the other $Y^{1''}$ is a hydrogen atom, or a salt thereof, which comprises treating a compound represented by the formula (I-1'):



(I-1')

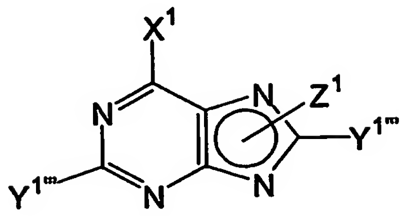
wherein

X^1 and Z^1 are as defined above, and

one of $Y^{1'}$ is a group represented by the formula: Me_2(OH)C-C≡C-, and the other $Y^{1'}$ is a hydrogen atom,

or a salt thereof, with a base (2).

[10] A production method of a compound represented by the formula (I-1'''):



(I-1''')

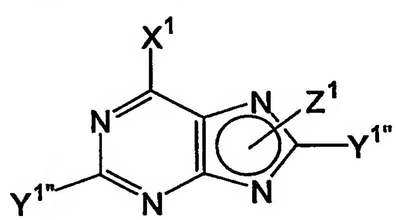
wherein

X^1 is an alkyl group, an alkoxy group, an aryl group, an optionally protected amino group, a halogen atom or a hydrogen atom,

Z^1 is an alkyl group, a sugar group, an amino-protecting group or a hydrogen atom, which is attached to a nitrogen atom at the 7- or 9-position of the purine nucleus, and

one of $Y^{1'''}$ is a group represented by the formula: A-C≡C-, wherein A is an aryl group optionally having substituents or a heterocyclic group optionally having substituents, and the other $Y^{1'''}$ is a hydrogen atom,

or a salt thereof, which comprises reacting a compound represented by the formula (I-1''):



(I-1'')

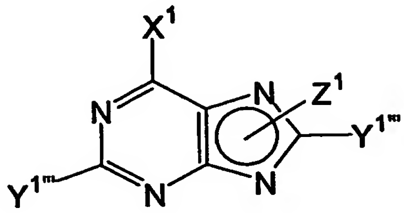
wherein

X^1 and Z^1 are as defined above, and

one of $Y^{1''}$ is a group represented by the formula: HC≡C-, and the other $Y^{1''}$ is a hydrogen atom,

or a salt thereof, with a compound represented by the formula (IV): A-X wherein A is as defined above, and X is a halogen atom, in the presence of a metal catalyst and a base (1).

[11] A production method of a compound represented by the formula (I-1'''):



(I-1''')

wherein

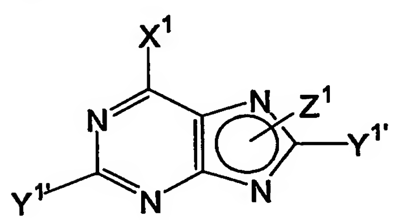
X^1 is an alkyl group, an alkoxy group, an aryl group, an optionally protected amino group, a halogen atom or a hydrogen atom,

one of $Y^{1'''}$ is a group represented by the formula: A-C≡C-, wherein A is an aryl group optionally having substituents or a heterocyclic group optionally having substituents, and the other $Y^{1'''}$ is a hydrogen atom, and

Z^1 is an alkyl group, a sugar group, an amino-protecting group or a hydrogen atom, which is attached to a nitrogen atom at the 7- or 9-position of the purine nucleus,

or a salt thereof, which comprises the following steps (a)-(c):

(a) a step of obtaining a compound represented by the formula (I-1'):



(I-1')

wherein

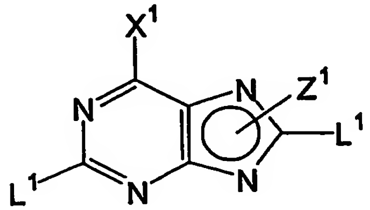
X^1 is an alkyl group, an alkoxy group, an aryl group, an optionally protected amino group, a halogen atom or a hydrogen atom,

Z^1 is an alkyl group, a sugar group, an amino-protecting group or a hydrogen atom, which is attached to a nitrogen atom at the 7- or 9-position of the purine nucleus, and

one of $Y^{1'}$ is a group represented by the formula: $Me_2(OH)C$-C≡C-,

and the other $Y^{1'}$ is a hydrogen atom,

or a salt thereof, which comprises reacting a compound represented by the formula (II-1):



(II-1)

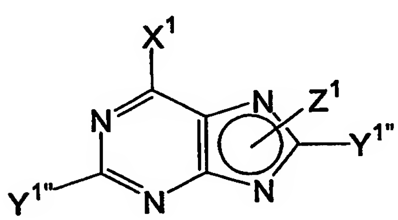
wherein

X^1 and Z^1 are as defined above, and

one of L^1 is a halogen atom, and the other L^1 is a hydrogen atom, provided that when X^1 is a halogen atom, L^1 is a halogen atom having higher leaving ability than the halogen atom represented by X^1,

or a salt thereof, with a compound represented by the formula (III): $Me_2(OH)C-C{\equiv}CH$, in the presence of a metal catalyst and a base (1),

(b) a step of obtaining a compound represented by the formula (I-1''):



(I-1'')

wherein

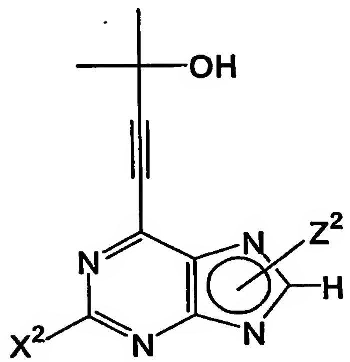
X^1 and Z^1 are as defined above, and

one of $Y^{1''}$ is a group represented by the formula: $HC{\equiv}C-$, and the other $Y^{1''}$ is a hydrogen atom, or a salt thereof, which comprises treating a compound of the formula (I-1') obtained in the step (a) or a salt thereof with a base (2), and

(c) a step of reacting a compound of the formula (I-1'') obtained in the step (b) or a salt thereof, with a compound represented by the formula (IV): A-X wherein A is an aryl

group optionally having substituents or a heterocyclic group optionally having substituents, and X is a halogen atom, in the presence of a metal catalyst and a base (1).

[12] A production method of a compound represented by the formula (I-2'):



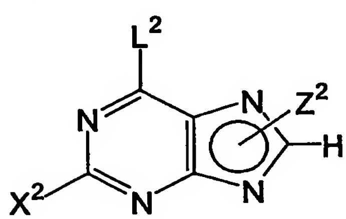
(I-2')

wherein

X^2 is an alkyl group, an alkoxy group, an aryl group, an optionally protected amino group, a halogen atom or a hydrogen atom, and

Z^2 is an alkyl group, a sugar group, an amino-protecting group or a hydrogen atom, which is attached to a nitrogen atom at the 7- or 9-position of the purine nucleus,

or a salt thereof, which comprises reacting a compound represented by the formula (II-2):



(II-2)

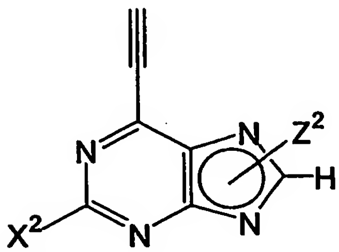
wherein

X^2 and Z^2 are as defined above, and

L^2 is a halogen atom, provided that when X^2 is a halogen atom, L^2 is a halogen atom having higher leaving ability than the halogen atom represented by X^2, or the same halogen atom as X^2, or a salt thereof, with a compound represented by the formula (III): $Me_2(OH)C\text{-}C{\equiv}CH$, in the presence of a metal catalyst and a

base (1).

[13] A production method of a compound represented by the formula (I-2''):



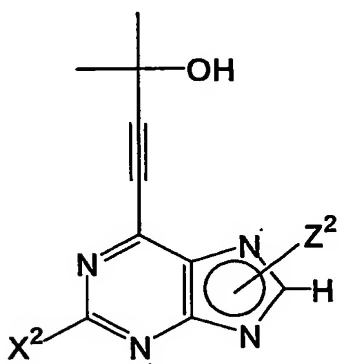
(I-2'')

wherein

X^2 is an alkyl group, an alkoxy group, an aryl group, an optionally protected amino group, a halogen atom or a hydrogen atom, and

Z^2 is an alkyl group, a sugar group, an amino-protecting group or a hydrogen atom, which is attached to a nitrogen atom at the 7- or 9-position of the purine nucleus,

or a salt thereof, which comprises treating a compound represented by the formula (I-2'):



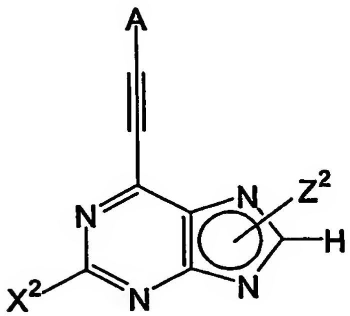
(I-2')

wherein

X^2 and Z^2 are as defined above,

or a salt thereof, with a base (2).

[14] A production method of a compound represented by the formula (I-2'''):



(I-2''')

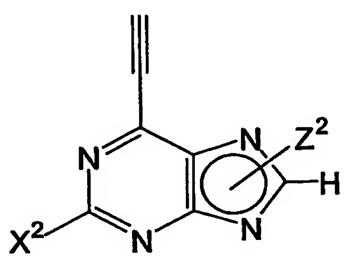
wherein

A is an aryl group optionally having substituents or a heterocyclic group optionally having substituents,

X^2 is an alkyl group, an alkoxy group, an aryl group, an optionally protected amino group, a halogen atom or a hydrogen atom, and

Z^2 is an alkyl group, a sugar group, an amino-protecting group or a hydrogen atom, which is attached to a nitrogen atom at the 7- or 9-position of the purine nucleus,

or a salt thereof, which comprises reacting a compound represented by the formula (I-2''):



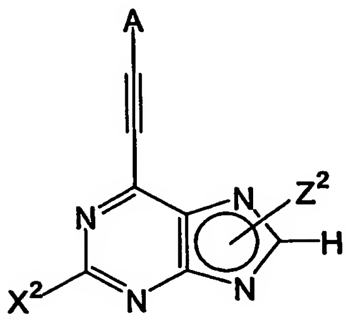
(I-2'')

wherein

X^2 and Z^2 are as defined above,

or a salt thereof, with a compound represented by the formula (IV): A-X, wherein A is as defined above, and X is a halogen atom, in the presence of a metal catalyst and a base (1).

[15] A production method of a compound represented by the formula (I-2'''):



(I-2''')

wherein

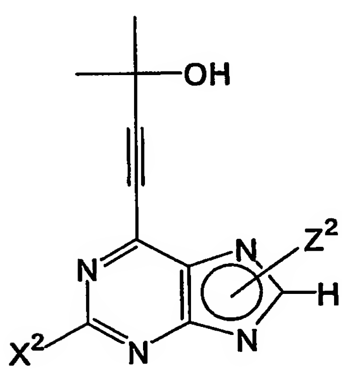
A is an aryl group optionally having substituents or a heterocyclic group optionally having substituents,

X^2 is an alkyl group, an alkoxy group, an aryl group, an optionally protected amino group, a halogen atom or a hydrogen atom, and

Z^2 is an alkyl group, a sugar group, an amino-protecting group or a hydrogen atom, which is attached to a nitrogen atom at the 7- or 9-position of the purine nucleus,

or a salt thereof, which comprises the following steps (a)-(c):

(a) a step of obtaining a compound represented by the formula (I-2'):



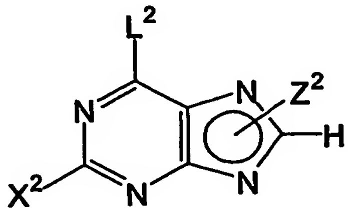
(I-2')

wherein

X^2 is an alkyl group, an alkoxy group, an aryl group, an optionally protected amino group, a halogen atom or a hydrogen atom, and

Z^2 is an alkyl group, a sugar group, an amino-protecting group or a hydrogen atom, which is attached to a nitrogen atom at the 7- or 9-position of the purine nucleus,

or a salt thereof, which comprises reacting a compound represented by the formula (II-2):



(II-2)

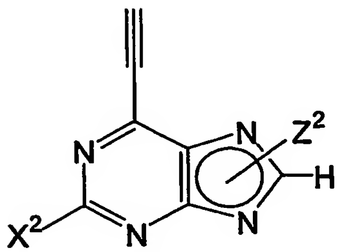
wherein

X^2 and Z^2 are as defined above, and

L^2 is a halogen atom, provided that when X^2 is a halogen atom, L^2 is a halogen atom having higher leaving ability than the halogen atom represented by X^2, or the same halogen atom as X^2,

or a salt thereof, with a compound represented by the formula (III): $Me_2(OH)C-C{\equiv}CH$, in the presence of a metal catalyst and a base (1),

(b) a step of obtaining a compound represented by the formula (I-2''):



(I-2'')

wherein

X^2 and Z^2 are as defined above,

or a salt thereof, which comprises treating a compound of the formula (I-2') obtained in the step (a) or a salt thereof, with a base (2), and

(c) a step of reacting a compound of the formula (I-2'') obtained in the step (b) or a salt thereof, with a compound represented by the formula (IV): A-X, wherein A is an aryl group optionally having substituents or a heterocyclic group optionally having substituents, and X is a halogen atom, in the presence of a metal catalyst and a base (1).

[16] The production method of any of the above-mentioned [8],

[10], [11], [12], [14] and [15], wherein the metal catalyst is a palladium compound.

[17] The production method of any of the above-mentioned [8], [10], [11], [12], [14] and [15], wherein the metal catalyst is a combination of a palladium compound and a copper compound.

[18] The production method of the above-mentioned [16] or [17], wherein the palladium compound is bis(triphenylphosphine)palladium dichloride or tetrakis(triphenylphosphine)palladium.

[19] The production method of the above-mentioned [17], wherein the copper compound is at least one selected from cuprous iodide, cuprous bromide and cuprous chloride.

[20] The production method of any of the above-mentioned [8], [10], [11], [12], [14] and [15]-[19], wherein the base (1) is an amine compound.

[21] The production method of the above-mentioned [20], wherein the amine compound is trialkylamine.

[22] The production method of the above-mentioned [21], wherein the trialkylamine is triethylamine or ethyldiisopropylamine.

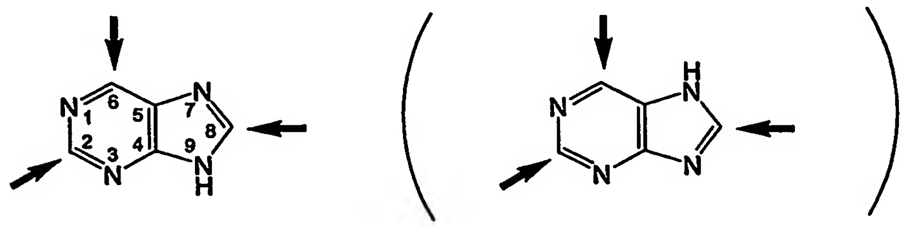
[23] The production method of any of the above-mentioned [9], [11], [13] and [15]-[22], wherein the base (2) is alkali metal hydroxide or alkali metal carbonate.

Best Mode for Embodying the Invention

The present invention is explained in detail in the following.

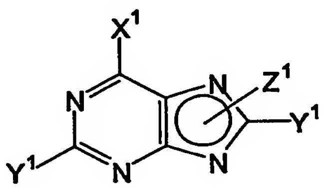
The present invention relates to an alkynylpurine compound represented by the following formula (I) wherein an alkynyl moiety is attached to any of the 2-, 6- and 8- positions of the purine nucleus shown with arrows (→), which is useful as an intermediate for the production of medicaments, (this compound encompasses isomers such as tautomer and the like, and optionally further has substituents

to be described in detail in the following), a salt thereof, and a production method thereof.

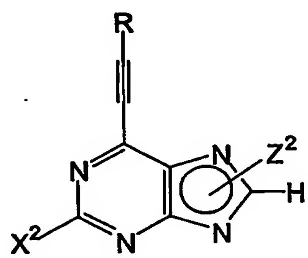


(I)

More specifically, this invention relates to a production method of an alkynylpurine compound represented by the formula (I-1) and the formula (I-2) (hereinafter to be referred to as compound (I-1) and compound (I-2)) and a salt thereof.



(I-1)



(I-2)

In the above-mentioned compound (I-1), X^1 is an alkyl group, an alkoxy group, an aryl group, an optionally protected amino group, a halogen atom or a hydrogen atom, one of Y^1 has, as an alkynyl moiety, a group represented by the formula: R-C≡C-, wherein R is a hydrogen atom, a hydrocarbon group optionally having substituents, an aryl group optionally having substituents or a heterocyclic group optionally having substituents, the other Y^1 is a hydrogen atom, and Z^1 is an alkyl group, a sugar group, an amino-protecting group or a hydrogen atom, which is attached to a nitrogen atom at the 7- or 9-position of the purine nucleus. In the above-mentioned compound (I-2), as an alkynyl moiety, a group represented by the formula: R-C≡C- [R is as defined above] is attached to the 6-position of the purine nucleus, X^2 is an alkyl group, an

alkoxy group, an aryl group, an optionally protected amino group, a halogen atom or a hydrogen atom, Z^2 is an alkyl group, a sugar group, an amino-protecting group or a hydrogen atom, which is attached to a nitrogen atom at the 7- or 9-position of the purine nucleus.

Definition

In the present invention, "R" is a hydrogen atom, a hydrocarbon group optionally having substituents, an aryl group optionally having substituents or a heterocyclic group optionally having substituents.

As the "hydrocarbon group" of the "hydrocarbon group optionally having substituents" denoted by R, for example, C_{1-10} alkyl (e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl etc.) and the like can be mentioned. Of these, C_{1-6} alkyl is preferable.

As the "substituent" of the above-mentioned "hydrocarbon group optionally having substituents", C_{1-6} alkyl (e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl etc.), hydroxy and the like can be mentioned. The kind, position and number of the substituents are not particularly limited.

As the above-mentioned "hydrocarbon group optionally having substituents", C_{1-6} alkyl optionally having substituents is preferable. Of those exemplified, C_{1-6} alkyl having hydroxy at the 1-position as a substituent is preferable. For example, 1-methyl-1-hydroxyethyl (i.e., $Me_2(OH)C-$) and the like are mentioned.

As the "aryl group" of the "aryl group optionally having substituents" denoted by R, for example, C_{6-12} aryl (e.g., phenyl, biphenylyl, naphthyl etc.) and the like are mentioned, with preference given to phenyl.

As the "substituent" of the above-mentioned "aryl group optionally having substituents", for example, halogen atoms (e.g., fluorine atom, chlorine atom, bromine atom, iodine atom etc.), C_{1-6} alkyl (e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, pentyl, hexyl etc.), C_{1-6} alkoxy (e.g., methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, tert-butoxy etc.), nitro and the like are mentioned. The kind, position and number of the substituents are not particularly limited.

As the above-mentioned "aryl group optionally having substituents", for example, phenyl; halophenyl such as chlorophenyl (e.g., 2- or 4-chlorophenyl etc.), fluorophenyl (e.g., 2- or 4-fluorophenyl etc.), bromophenyl (e.g., 2- or 4-bromophenyl etc.) and the like; C_{1-6} alkylphenyl (e.g., 3- or 4-methylphenyl etc.); C_{1-6} alkoxyphenyl (e.g., 4-methoxyphenyl etc.); nitrophenyl (e.g., 4-nitrophenyl etc.) and the like are preferable.

As the "heterocyclic group" of the "heterocyclic group optionally having substituents" denoted by R, for example, 5 to 8-membered heterocyclic groups containing, besides carbon atoms, 1 to 3 hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atom are mentioned. As R, nitrogen-containing heterocyclic groups such as pyridyl (e.g., pyridin-3-yl etc.), pyrimidyl (e.g., pyrimidin-2-yl, pyrimidin-3-yl, pyrimidin-5-yl etc.) and the like are particularly preferable.

As the "substituent" of the above-mentioned "heterocyclic group optionally having substituents", for example, halogen atoms (e.g., fluorine atom, chlorine atom, bromine atom, iodine atom etc.), oxo and the like are mentioned. The kind, position and number of the substituents are not particularly limited.

As the above-mentioned "heterocyclic group optionally

having substituents", for example, pyridin-3-yl, 2,4-dioxopyrimidin-5-yl and the like are preferable.

As R, preferred are hydrogen atom, a hydrocarbon group optionally having substituents and an aryl group optionally having substituents, more preferred are hydrogen atom, C_{1-6} alkyl optionally having substituents and C_{6-12} aryl optionally having substituents, and still more preferred are hydrogen atom and C_{1-6} alkyl optionally having substituents.

More specifically, hydrogen atom and C_{1-6} alkyl having hydroxy at the 1-position as a substituent (e.g., 1-methyl-1-hydroxyethyl) are particularly preferable as R.

The reason for particular preference of hydrogen atom as R is that, when R is a hydrogen atom, the alkynyl moiety represented by R-C≡C- (i.e., ethynyl group) is still more easily modified due to its high reactivity [see Step C described in detail in the following].

The reason for particular preference of the "C_{1-6} alkyl having hydroxy at the 1-position" as R is that, when R is "C_{1-6} alkyl having hydroxy at the 1-position", the alkynyl moiety represented by R-C≡C- can be easily converted to an ethynyl group via β-elimination by a treatment with a base [see the treatment with base (2) in Step B explained in the following].

In the present invention, "X^1" and "X^2" are each an alkyl group, an alkoxy group, an aryl group, an optionally protected amino group, a halogen atom or a hydrogen atom.

As the "alkyl group" denoted by "X^1" and "X^2", for example, C_{1-10} alkyl (e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl etc.) and the like are mentioned for both.

As the "alkoxy group" denoted by "X^1" and "X^2", for example, C_{1-6} alkoxy (e.g., methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, tert-butoxy etc.) and the like are mentioned for both.

As the "aryl group" denoted by "X^1" and "X^2", for example, C_{6-12} aryl (e.g., phenyl, biphenylyl, naphthyl etc.) and the like are mentioned for both.

The "protecting group" of the "optionally protected amino group" denoted by "X^1" and "X^2" is not particularly limited as long as it is an amino-protecting group known to those of ordinary skill in the art of the organic chemistry, and, for example, a hetero ring group (e.g., a 5 to 8-membered hetero ring group containing, besides carbon atoms, 1 to 3 hetero atoms selected from the group consisting of nitrogen atom, oxygen atom and sulfur atom, such as tetrahydropyranyl (e.g., tetrahydropyran-2-yl etc.) and the like), C_{7-15} aralkyl (e.g., benzyl etc.), C_{1-5} acyl (e.g., acetyl etc.), trialkylsilyl (e.g., trimethylsilyl etc.), carbamate (e.g., tert-butylcarbamate) and the like are mentioned.

The "amino group" of the "optionally protected amino group" denoted by "X^1" and "X^2" is optionally substituted by 1 or 2 substituents. As the substituent, for example, C_{1-6} alkyl (e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, pentyl, hexyl etc.), C_{6-12} aryl (e.g., phenyl, naphthyl etc.) and the like are mentioned. When the amino group has two substituents, the substituents may be the same or different.

As the "halogen atom" denoted by "X^1" and "X^2", for example, fluorine atom, chlorine atom, bromine atom, iodine atom and the like are mentioned, particularly preferably chlorine atom.

In a compound represented by the formula (I-1) in the present specification, one of "Y^1" is a group represented by the formula: R-C≡C- wherein R is as defined above), and the other "Y^1" is a hydrogen atom.

In a compound represented by the formula (I-1') in the present specification, one of "$Y^{1'}$" is a group represented by

the formula: $Me_2(OH)C-C\equiv C-$, and the other "$Y^{1'}$" is a hydrogen atom.

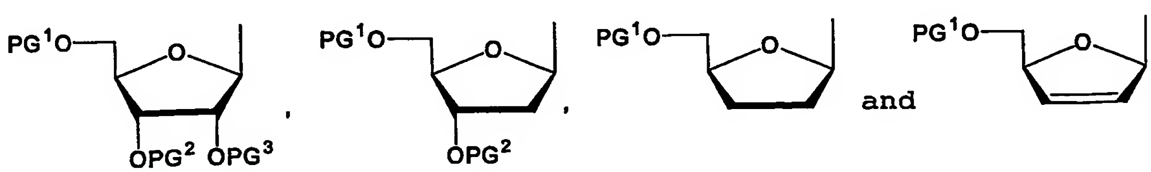
In a compound represented by the formula (I-1'') in the present specification, one of "$Y^{1''}$" is a group represented by the formula: $HC\equiv C-$, and the other "$Y^{1''}$" is a hydrogen atom.

In a compound represented by the formula (I-1''') in the present specification, one of "$Y^{1'''}$" is a group represented by the formula: $A-C\equiv C-$ wherein A is as defined in the following "A-X"), and the other "$Y^{1'''}$" is a hydrogen atom.

The "Z^1" and "Z^2" are each an alkyl group, a sugar group, an amino-protecting group or a hydrogen atom, which is attached to a nitrogen atom at the 7- or 9-position of the purine nucleus.

As the "alkyl group" denoted by "Z^1" and "Z^2", for example, C_{1-6} alkyl (e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl etc.) and the like are mentioned for both.

As the "sugar group" denoted by "Z^1" and "Z^2", for example, pentoses (including furanoses, pyranoses and all isomers thereof, wherein hydroxy groups of the sugar are each independently may be protected by a "hydroxy protecting-group" well known to those of ordinary skill in the art of the organic synthesis and the carbon atom at the 1-position of the sugar is directly attached to the nitrogen atom at the 7- or 9-position of the purine nucleus) is exemplified. Of those,



are preferable, wherein PG^1, PG^2 and PG^3 are the same or different and each is independently a hydroxy-protecting group or a hydrogen atom.

The hydroxy-protecting group is not particularly limited as long as it is a hydroxy-protecting group well known to those of ordinary skill in the art of the organic synthesis, and, for example, C_{1-5} acyl (e.g., acetyl etc.), C_{7-15} aralkyl (e.g., benzyl group etc.), trialkylsilyl (e.g., trimethylsilyl etc.) and the like are mentioned.

As the "amino-protecting group" denoted by "Z^1" and "Z^2", amino-protecting groups well known to those of ordinary skill in the art of the organic synthesis can be used. As the amino-protecting group, for example, hetero ring group (e.g., 5 to 8-membered hetero ring group containing, besides carbon atoms, 1 to 3 hetero atoms selected from the group consisting of nitrogen atom, oxygen atom and sulfur atom, such as tetrahydropyranyl (e.g., tetrahydropyran-2-yl etc.) and the like), C_{7-15} aralkyl (e.g., benzyl etc.), C_{1-5} acyl (e.g., acetyl etc.), trialkylsilyl (e.g., trimethylsilyl etc.), carbamate (e.g., tert-butylcarbamate) and the like are mentioned.

The "Z^1" and "Z^2" are each preferably a hydrogen atom and an amino-protecting group, and as the amino-protecting group, a hetero ring group is preferable, and tetrahydropyranyl (e.g., tetrahydropyran-2-yl etc.) is particularly preferable. As the amino-protecting group, C_{7-15} aralkyl is also preferable, and benzyl is particularly preferable.

In a compound represented by the formula (II-1) in the present specification, one of "L^1" is a halogen atom (e.g., fluorine atom, chlorine atom, bromine atom, iodine atom etc.), and the other "L^1" is a hydrogen atom. However, when X^1 is a halogen atom, one of L^1 is a "halogen atom having higher leaving ability than the halogen atom represented by X^1".

In a compound represented by the formula (II-2) in the present specification, "L^2" is a halogen atom (e.g., fluorine atom, chlorine atom, bromine atom, iodine atom etc.). However, when X^2 is a halogen atom, L^2 is a "halogen atom having higher

leaving ability than the halogen atom represented by X^2", or the "same halogen atom as X^2". When X^2 is a halogen atom in a compound represented by the formula (II-2), L^2 may be the "same halogen atom as X^2" because, when the same halogen atoms are present at the 2- and 6-positions of the purine nucleus, the halogen atom at the 6-position generally has higher leaving ability than the halogen atom at the 2-position.

The above-mentioned "halogen atom having higher leaving ability than the halogen atom represented by X^1" and "halogen atom having higher leaving ability than the halogen atom represented by X^2" each mean a halogen atom having higher leaving ability than the halogen atom represented by X^1 or X^2, according to the leaving ability of halogen atom: F<Cl<Br<I. For example, when X^1 and X^2 are each a fluorine atom, L^1 and L^2 are each selected from the group consisting of chlorine atom, bromine atom and iodine atom, when X^1 and X^2 are each a chlorine atom, L^1 and L^2 are each a bromine atom or an iodine atom, when X^1 and X^2 are each a bromine atom and L^1 and L^2 are each an iodine atom.

When X^1 and X^2 are each a halogen atom, it is particularly preferable that X^1 and X^2 be each a chlorine atom and L^1 and L^2 be each an iodine atom, in view of the difference in leaving ability and easiness of modification thereafter.

When X^1 and X^2 are each other than a halogen atom, L^1 and L^2 are not particularly limited, and a halogen atom generally having higher leaving ability, particularly an iodine atom, is preferable.

In the compound represented by "A-X" in the present invention [i.e. a compound represented by the formula (IV)], "A" is an aryl group optionally having substituents or a heterocyclic group optionally having substituents and "X" is a halogen atom.

The "aryl group optionally having substituents" and

"heterocyclic group optionally having substituents" denoted by "A" are each the same as the "aryl group optionally having substituents" and "heterocyclic group optionally having substituents" denoted by the above-mentioned "R".

As the "halogen atom" denoted by "X", for example, fluorine atom, chlorine atom, bromine atom, iodine atom and the like are mentioned, with preference given to bromine atom and iodine atom from the aspect of reactivity.

As the compound represented by the formula (IV): A-X, dihalobenzene (e.g., 1-bromo-4-chlorobenzene, 2-chloro-4-iodobenzene, 1-chloro-2-iodobenzene, 1-fluoro-2-iodobenzene etc.), C_{1-6} alkylhalobenzene (e.g., 4-bromotoluene, 4-iodotoluene, 3-bromotoluene, 3-iodotoluene etc.), C_{1-6} alkoxyhalobenzene (e.g., 4-bromoanisole, 4-iodoanisole etc.), nitrohalobenzene (e.g., 1-bromo-4-nitrobenzene, 1-iodo-4-nitrobenzene etc.), halopyridine (e.g., 3-bromopyridine, 3-iodopyridine etc.) and dioxohalopyrimidine (e.g., 2,4-dioxo-5-iodopyrimidine etc.) are particularly preferable.

As the "metal catalyst" to be used in the present invention, a palladium compound and a combination of a palladium compound and a copper compound are mentioned.

As the "palladium compound" to be used in the present invention, bis(triphenylphosphine)palladium dichloride [i.e. $(Ph_3P)_2PdCl_2$], tetrakis(triphenylphosphine)palladium [i.e. $(Ph_3P)_4Pd$], palladium acetate [i.e. $Pd(OAc)_2$], bis(acetylacetonato)palladium [i.e. $Pd(acac)_2$], [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) chloride [i.e. $PdCl_2(dppf)_2$] and the like are mentioned. Of these, bis(triphenylphosphine)palladium dichloride and tetrakis(triphenylphosphine)palladium are preferable, from the aspect of solubility in a solvent.

When a combination of a palladium compound and a copper compound is used as a metal catalyst, the palladium compound

includes by the aforementioned palladium catalysts and, from the aspect of solubility in a solvent, bis(triphenylphosphine)palladium dichloride is particularly preferable. When a combination of a palladium compound and a copper compound is used as a metal catalyst, as the "copper compound", for example, cuprous halide such as cuprous iodide, cuprous bromide, cuprous chloride and the like and cuprous cyanide are mentioned. Of these, cuprous halide is preferable, and cuprous iodide is particularly preferable in view of the catalytic ability. In the present invention, two or more kinds of copper compounds may be used.

When a palladium compound and a copper compound are used in combination as a metal catalyst, the kind of the palladium compound and copper compound to be used is not particularly limited, and from the above-mentioned aspects, a combination of bis(triphenylphosphine)palladium dichloride and cuprous iodide is particularly preferable.

As the "base (1)" to be used in the present invention, for example, amine compound, alkali metal hydroxide, alkali metal carbonate, basic heterocyclic compound and the like are mentioned.

As the "amine compound", for example, trialkylamine and the like are mentioned, wherein the alkyl moiety of the trialkylamine is, for example, C_{1-6} alkyl (e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl etc.), and the alkyl groups may be the same or different. As trialkylamine, for example, triethylamine, ethyldiisopropylamine and the like are mentioned.

As the "alkali metal hydroxide", for example, sodium hydroxide, potassium hydroxide and the like are mentioned.

As the "alkali metal carbonate", for example, sodium carbonate, potassium carbonate and the like are mentioned.

As the "basic heterocyclic compound", for example,

pyridine and the like are mentioned.

As the "base (1)" to be used in the present invention, amine compound is preferable. As the amine compound, trialkylamine is preferable, and particularly preferred therefrom are triethylamine and ethyldiisopropylamine.

As the "base (2)" to be used in the present invention, for example, alkali metal hydroxide, alkali metal carbonate, amine and the like are mentioned.

As the "alkali metal hydroxide", for example, sodium hydroxide, potassium hydroxide and the like are mentioned.

As the "alkali metal carbonate", for example, sodium carbonate, potassium carbonate, sodium hydrogencarbonate and the like are mentioned.

As the "amine", for example, triethylamine and the like are mentioned.

As the "base (2)" to be used in the present invention, alkali metal hydroxide and alkali metal carbonate are preferable. Of these, alkali metal hydroxide is preferable, and sodium hydroxide and potassium hydroxide are particularly preferable, in view of the solubility in water.

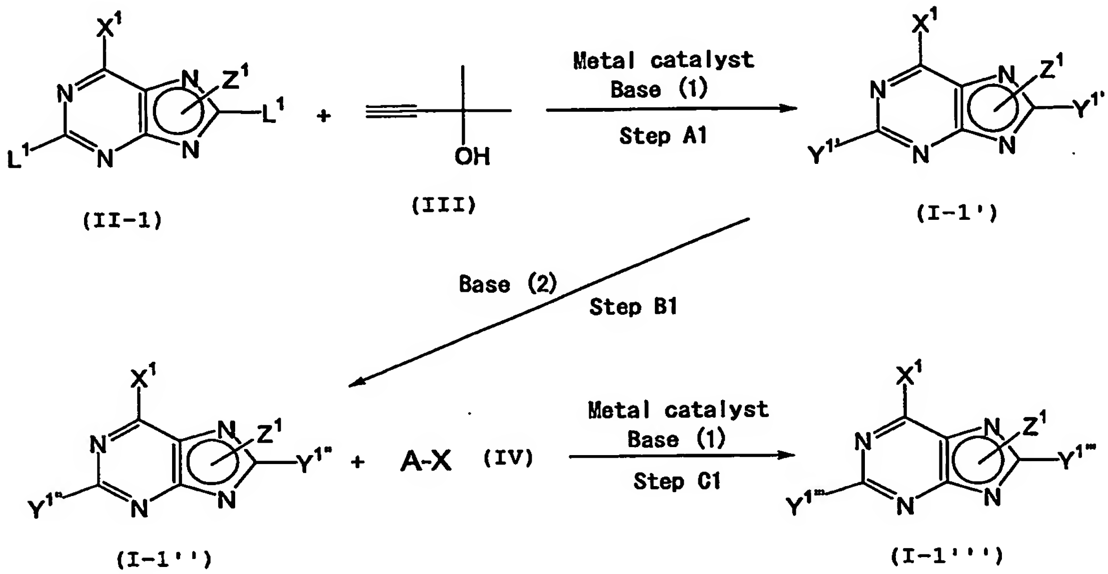
The salts of the compound according to the present invention are not particularly limited, and, for example, a salt of the compound according to the present invention with an organic acid (e.g., methanesulfonic acid, trifluoromethanesulfonic acid, p-toluenesulfonic acid etc.), a salt of the compound according to the present invention with an inorganic acid (e.g., hydrochloric acid, sulfuric acid, phosphoric acid, nitric acid etc.), and ammonium salt of the compound according to the present invention (e.g., tetraalkylammonium salt etc.) and the like are mentioned.

Production method of alkynylpurine compound

The production method of the alkynylpurine compound

according to the present invention is explained in the following.

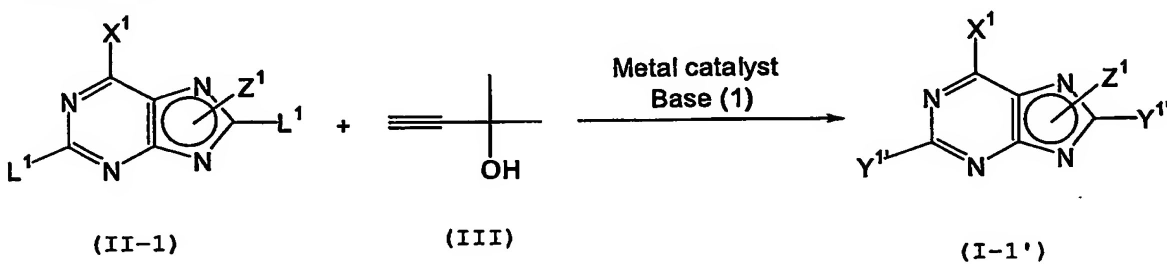
First, the production methods of the alkynylpurine compound represented by the above-mentioned formula (I-1) are explained by referring to the following Scheme 1.



Scheme 1

In the Scheme, each symbol is as defined above.

(Step A1)



wherein each symbol is as defined above.

In Step A1, a compound represented by the formula (I-1′) wherein one of $Y^{1'}$ is $Me_2(OH)C\text{-}C{\equiv}C\text{-}$ and the other $Y^{1'}$ is a hydrogen atom (hereinafter sometimes to be referred to as compound (I-1′)) or a salt thereof is obtained by reacting a compound represented by the formula (II-1) wherein one of L^1 is a halogen atom and the other L^1 is a hydrogen atom (hereinafter sometimes to be referred to as compound (II-1)) or a salt

thereof, with a compound represented by the formula (III) (hereinafter sometimes to be referred to as compound (III)), in the presence of a metal catalyst and a base (1).

In Step A1, a palladium compound may be used alone as a metal catalyst, as defined above. When a palladium compound is used alone, the palladium compound is particularly preferably bis(triphenylphosphine)palladium dichloride. The amount of the palladium compound to be used is not particularly limited as long as a catalytic amount relative to compound (II-1) or a salt thereof is used. It is generally 0.01-1.0 mmole, preferably 0.05-0.2 mmole, per 1 mmole of compound (II-1) or a salt thereof. As the metal catalyst, a combination of a palladium compound and a copper compound is preferable, in view of the activity of the catalyst. When the palladium compound and the copper compound are to be used in combination, bis(triphenylphosphine)palladium dichloride is particularly preferable as the palladium compound, and cuprous iodide is particularly preferable as the copper compound. The amount of the palladium compound to be used and the amount of the copper compound to be used are not particularly limited as long as a catalytic amount relative to compound (II-1) or a salt thereof is used. The amount of the palladium compound to be used is generally 0.01-1.0 mmole, preferably 0.05-0.2 mmole, per 1 mmole of compound (II-1) or a salt thereof, and the amount of the copper compound to be used is generally 0.01-1.0 mmole, preferably 0.05-0.2 mmole, per 1 mmole of compound (II-1) or a salt thereof.

In Step A1, an amine compound is preferably used as the base (1), as defined above. In addition, trialkylamine is preferably used as an amine compound. As the trialkylamine, triethylamine and ethyldiisopropylamine are preferable. The amount of the base (1) to be used is generally 1.0-5.0 mmole, preferably 1.0-1.5 mmole, per 1 mmole of compound (II-1) or a

salt thereof.

The compound (II-1) or a salt thereof to be used in Step A1 can be synthesized according to the method described in, for example, US 4,719,295 to Cook et al., and a method analogous thereto.

The compound (III) to be used in Step A1 is commercially available.

The salt of compound (II-1) to be used in Step A1 is not particularly limited, and, for example, a salt of compound (II-1) with an organic acid (e.g., methanesulfonic acid, trifluoromethanesulfonic acid, p-toluenesulfonic acid etc.), a salt of compound (II-1) with an inorganic acid (e.g., hydrochloric acid, sulfuric acid, phosphoric acid, nitric acid etc.), and ammonium salt thereof (e.g., tetraalkylammonium salt etc.) and the like are mentioned.

In Step A1, the amount of compound (III) to be used is generally 1.0-5.0 mmole, preferably 1.0-1.5 mmole, per 1 mmole of compound (II-1) or a salt thereof.

In Step A1, the solvent is not particularly limited as long as the reaction is not adversely affected by the solvent, and, for example, aprotic solvents such as DMF (N,N-dimethylformamide), DMSO (dimethyl sulfoxide), N,N-dimethylacetamide, THF (tetrahydrofuran) and the like, and the like are mentioned. Of these, DMF is preferable. The amount of the solvent to be used is not particularly limited and it is generally 1.5-100 mL, preferably 1.5-50 mL, per 1 mmole of compound (II-1) or a salt thereof.

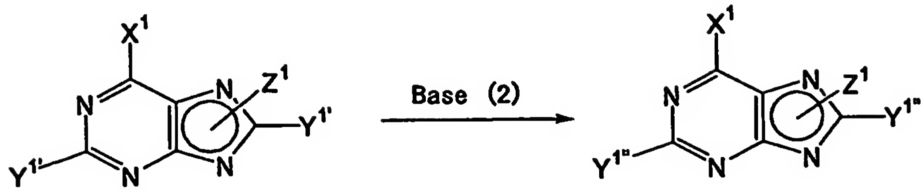
In Step A1, the reaction time varies depending on the reagents and the solvent to be used, and is generally 1-5 hrs.

In Step A1, the reaction temperature varies depending on the reagents and the solvent to be used, and is generally 40°C-150°C, preferably 80°C-100°C.

As the salt of compound (I-1'), those similar to the

salts recited above are mentioned.

(Step B1)



(I-1')   (I-1'')

wherein each symbol is as defined above.

In Step B1, a compound represented by the formula (I-1'') wherein one of $Y^{1''}$ is HC≡C- and the other $Y^{1''}$ is a hydrogen atom (hereinafter sometimes to be referred to as compound (I-1'')) or a salt thereof is obtained by treating compound (I-1') obtained in the above-mentioned Step A1, wherein one of $Y^{1'}$ is $Me_2(OH)C$-C≡C-, and the other $Y^{1'}$ is a hydrogen atom, or a salt thereof with a base (2).

In Step B1, alkali metal hydroxide is particularly preferably used as the base (2), as defined above. Particularly, sodium hydroxide and potassium hydroxide are preferable.

In Step B1, the amount of the base (2) to be used is generally 1-20 mmole, preferably 3-10 mmole, per 1 mmole of compound (I-1') or a salt thereof.

In Step B1, the solvent is not particularly limited as long as the reaction is not adversely affected by the solvent, and, for example, aprotic solvents such as toluene, xylene, THF, MTBE (tert-butylmethyl ether) and the like, and the like are mentioned, with particular preference given to toluene. The amount of the solvent to be used is not particularly limited, and is generally 10-500 mL, preferably 50-200 mL, per 1 mmole of compound (I-1') or a salt thereof.

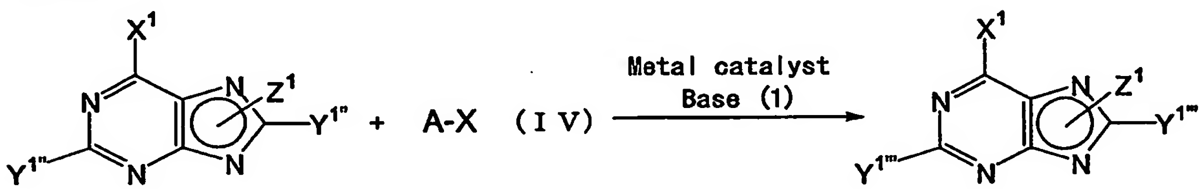
In Step B1, the reaction time varies depending on the reagents and the solvent to be used, and is generally 1-5 hrs.

In Step B1, the reaction temperature varies depending on

the substrate as well as the reagents and the solvent to be used, and is generally 30°C-150°C, preferably 60°C-110°C. Particularly when compound (I-1') has $Me_2(OH)C-C\equiv C-$ at the 8-position, the reaction temperature is preferably 60°C-80°C, because the reaction rate becomes higher.

As the salt of compound (I-1''), those similar to the salts recited above are mentioned.

(Step C1)



(I-1'') (I-1''')

wherein each symbol is as defined above.

In Step C1, a compound represented by the formula (I-1''') wherein one of $Y^{1'''}$ is $A-C\equiv C-$ and the other $Y^{1'''}$ is a hydrogen atom (hereinafter sometimes to be referred to as compound (I-1''')) or a salt thereof is obtained by reacting, in the presence of a metal catalyst and a base (1), compound (I-1'') obtained in Step B1, wherein one of $Y^{1''}$ is $HC\equiv C-$ and the other $Y^{1''}$ is a hydrogen atom, or a salt thereof with a halide compound represented by the formula (IV) (hereinafter sometimes to be referred to as compound (IV)).

In Step C1, a palladium compound may be used alone as a metal catalyst, as defined above. When a palladium compound is used alone, a palladium compound is particularly preferably bis(triphenylphosphine)palladium dichloride. The amount of the palladium compound to be used is not particularly limited as long as a catalytic amount relative to compound (I-1'') or a salt thereof is used, and is generally 0.01-1.0 mmole, preferably 0.05-0.2 mmole, per 1 mmole of compound (I-1'') or a salt thereof. As a metal catalyst, a combination of a

palladium compound and a copper compound is preferable. When a palladium compound and a copper compound are used in combination, bis(triphenylphosphine)palladium dichloride is a particularly preferable palladium compound, and cuprous iodide is a particularly preferable copper compound. The amount of the palladium compound to be used and the amount of the copper compound to be used are not particularly limited as long as a catalytic amount is used relative to compound (I-1'') or a salt thereof. The amount of the palladium compound to be used is generally 0.01-1.0 mmole, preferably 0.05-0.2 mmole, per 1 mmole of compound (I-1'') or a salt thereof, and the amount of the copper compound to be used is generally 0.01-1.0 mmole, preferably 0.05-0.2 mmole, per 1 mmole of compound (I-1'') or a salt thereof.

In Step C1, an amine compound is preferably used as a base (1), as defined above. As the amine compound, trialkylamine is preferable. As the trialkylamine, triethylamine and ethyldiisopropylamine are preferable. The amount of the base (1) to be used is generally 1.0-5.0 mmole, preferably 1.0-3.0 mmole, per 1 mmole of compound (I-1'') or a salt thereof.

In Step C1, the amount of compound (IV) to be used is generally 1.0-2.0 mmole, preferably 1.0-1.3 mmole, per 1 mmole of compound (I-1'') or a salt thereof.

In Step C1, the solvent is not particularly limited as long as the reaction is not adversely affected by the solvent, and, for example, aprotic solvents such as DMF, N,N-dimethylacetamide, DMSO, THF and the like, and the like are mentioned, with preference given to DMF. The amount of the solvent to be used is not particularly limited, and is generally 1-200 mL, preferably 5-20 mL, per 1 mmole of compound (I-1'') or a salt thereof.

In Step C1, the reaction time varies depending on the

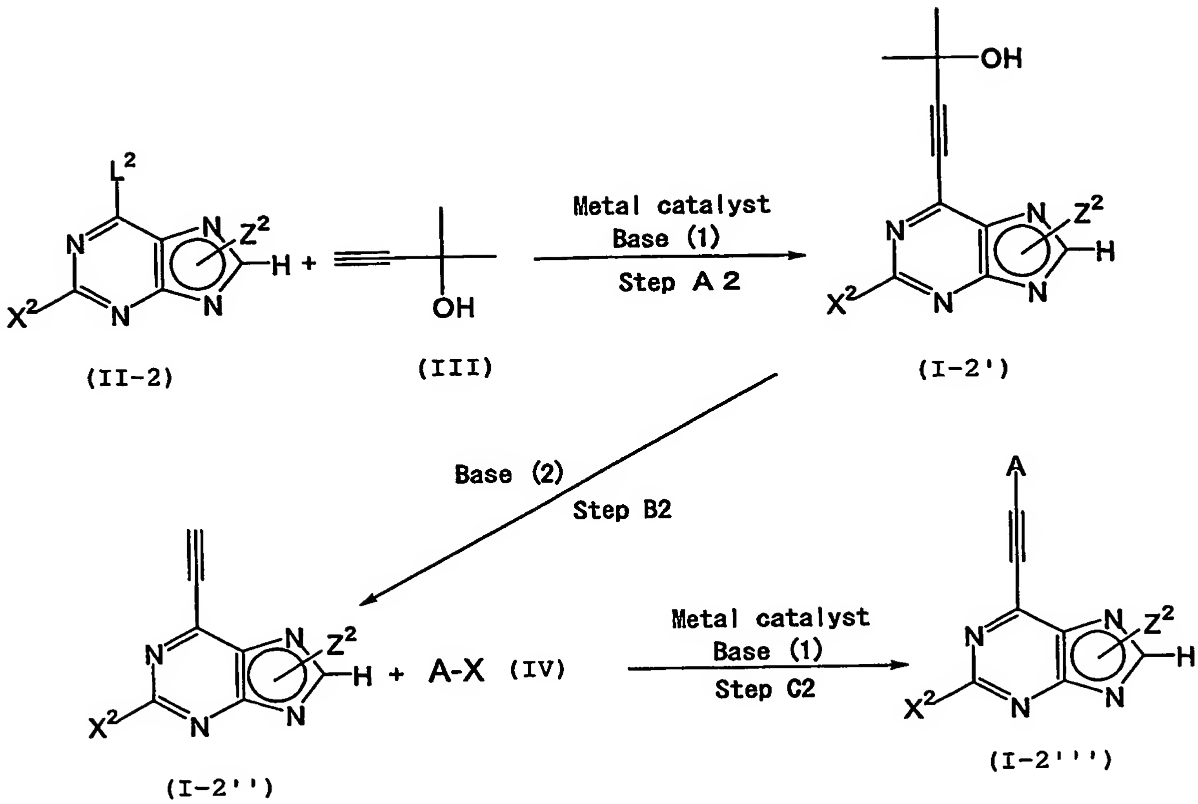
reagents and solvent to be used, and is generally 2-8 hrs.

In Step C1, the reaction temperature varies depending on the reagents and the solvent to be used, and is generally 50°C-150°C, preferably 80°C-100°C.

As the salt of compound (I-1'''), those similar to the salts recited above are mentioned.

Accordingly, alkynylpurine compound represented by the formula (I-1) is considered to encompass compounds (I-1'), (I-1''), (I-1''') (including isomers such as tautomer and the like, obtainable in each step) and salts thereof obtained by the reactions described in Scheme 1, as well as compounds and salts thereof obtained by the methods according to Scheme 1.

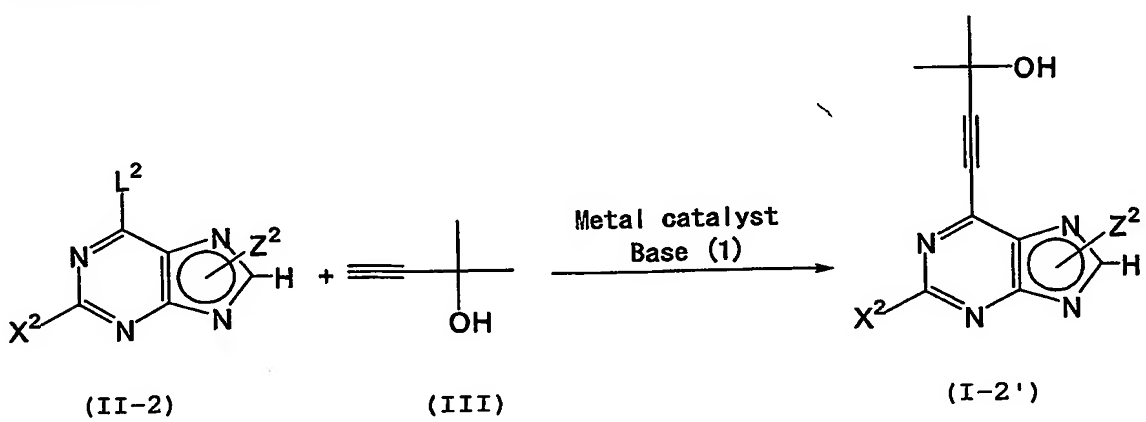
As with the production methods of the alkynylpurine compound represented by the formula (I-1), the production methods of the alkynylpurine compound represented by the above-mentioned formula (I-2) are explained in the following while referring to the following Scheme 2.



Scheme 2

In the Scheme, each symbol is as defined above.

(Step A2)



wherein each symbol is as defined above.

In Step A2, a compound represented by the formula (I-2') (hereinafter sometimes to be referred to as compound (I-2')) or a salt thereof is obtained by reacting a compound represented by the formula (II-2) wherein L^2 is a halogen atom

(hereinafter sometimes to be referred to as compound (II-2)) or a salt thereof with compound (III), in the presence of a metal catalyst and a base (1).

In Step A2, a palladium compound may be used alone as a metal catalyst, as defined above. When a palladium compound is to be used alone, the palladium compound is particularly preferably bis(triphenylphosphine)palladium dichloride. The amount of the palladium compound to be used is not particularly limited as long as a catalytic amount is used relative to compound (II-2) or a salt thereof, and is generally 0.01-1.0 mmole, preferably 0.05-0.2 mmole, per 1 mmole of compound (II-2) or a salt thereof. As a metal catalyst, a combination of a palladium compound and a copper compound is preferable. When a palladium compound and a copper compound are used in combination, bis(triphenylphosphine)palladium dichloride is particularly preferable as a palladium compound, and cuprous iodide is particularly preferable as a copper compound. The amount of the palladium compound to be used and the amount of the copper compound to be used are not particularly limited as long as a catalytic amount is used relative to compound (II-2) or a salt thereof, and the amount of the palladium compound to be used is generally 0.01-1.0 mmole, preferably 0.05-0.2 mmole, per 1 mmole of compound (II-2) or a salt thereof, and the amount of the copper compound to be used is generally 0.01-1.0 mmole, preferably 0.05-0.2 mmole, per 1 mmole of compound (II-2) or a salt thereof.

In Step A2, an amine compound is preferably used as a base (1), as defined above. As the amine compound, trialkylamine is preferable. As the trialkylamine, triethylamine and ethyldiisopropylamine are preferable. The amount of the base (1) to be used is generally 1.0-5.0 mmole, preferably 1.0-1.5 mmole, per 1 mmole of compound (II-2) or a

salt thereof.

The salt of compound (II-2) used in Step A2 is not particularly limited and, for example, a salt of compound (II-2) with an organic acid (e.g., methanesulfonic acid, trifluoromethanesulfonic acid, p-toluenesulfonic acid etc.), a salt of compound (II-2) with an inorganic acid (e.g., hydrochloric acid, sulfuric acid, phosphoric acid, nitric acid etc.), ammonium salt thereof (e.g., tetraalkylammonium salt etc.) and the like are mentioned.

In Step A2, the amount of compound (III) to be used is, generally 1.0-5.0 mmole, preferably 1.0-1.5 mmole, per 1 mmole of compound (II-2) or a salt thereof.

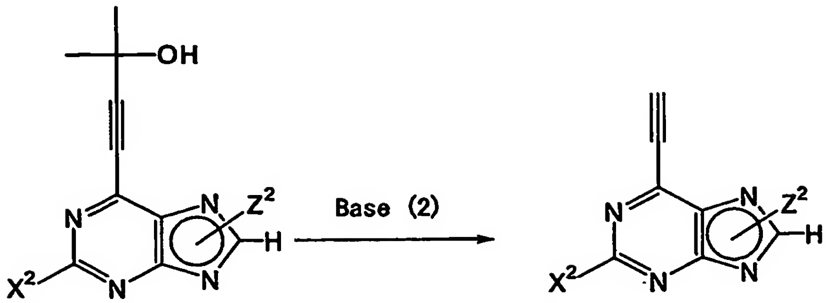
In Step A2, the solvent is not particularly limited as long as the reaction is not adversely affected by the solvent, and, for example, aprotic solvents such as DMF, DMSO, N,N-dimethylacetamide, THF and the like, and the like are mentioned, with preference given to DMF. The amount of the solvent to be used is not particularly limited, and is generally 0.5-10 mL, preferably 1-5 mL, per 1 mmole of compound (II-2) or a salt thereof.

In Step A2, the reaction time varies depending on the reagents and the solvent to be used, and is generally 1-5 hrs.

In Step A2, the reaction temperature varies depending on the reagents and the solvent to be used, and is generally 40°C-150°C, preferably 80°C-100°C.

As the salt of compound (I-2'), the salts recited above are mentioned.

(Step B2)



(I-2')

(I-2'')

wherein each symbol is as defined above.

In Step B2, a compound represented by the formula (I-2'') (hereinafter sometimes to be referred to as compound (I-2'')) or a salt thereof is obtained by treating compound (I-2') obtained in the above-mentioned Step A2 or a salt thereof with a base (2).

In Step B2, alkali metal hydroxide is particularly preferably used as the base (2), as defined above, with preference given to sodium hydroxide and potassium hydroxide.

In Step B2, the amount of base (2) to be used is generally 1-20 mmole, preferably 3-10 mmole, per 1 mmole of compound (I-2') or a salt thereof.

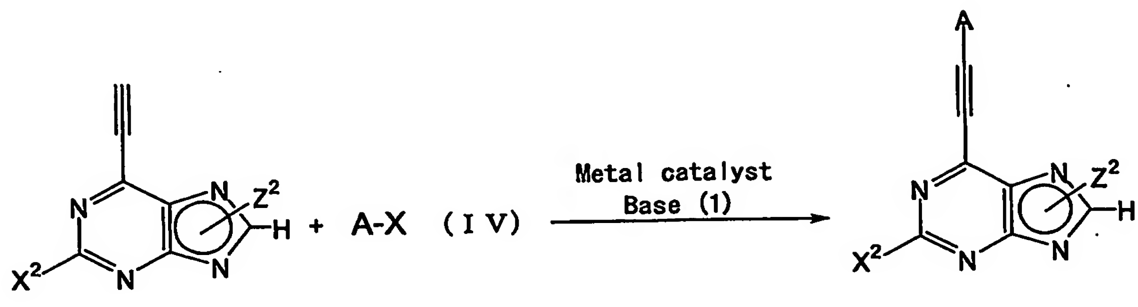
In Step B2, the solvent is not particularly limited as long as the reaction is not adversely affected by the solvent, and, for example, aprotic solvents such as toluene, xylene, THF, MTBE and the like, and the like are mentioned, with preference given to toluene. The amount of the solvent to be used is not particularly limited, and is generally 10-500 mL, preferably 50-200 mL, per 1 mmole of compound (I-2') or a salt thereof.

In Step B2, the reaction time varies depending on the reagents and the solvent to be used, and is generally 1-5 hrs.

In Step B2, the reaction temperature varies depending on the reagents and the solvent to be used, and is generally 60°C-150°C, preferably 90°C-110°C.

As the salt of compound (I-2''), those similar to the salts recited above are mentioned.

(Step C2)



(I-2'') (I-2''')

wherein each symbol is as defined above.

In Step C2, a compound represented by the formula (I-2''') (hereinafter sometimes to be referred to as compound (I-2''')) or a salt thereof is obtained by reacting compound (I-2'') obtained in the above-mentioned Step B2 or a salt thereof with compound (IV), in the presence of a metal catalyst and a base (1).

In Step C2, a palladium compound may be used alone as a metal catalyst, as defined above. When a palladium compound is used alone, bis(triphenylphosphine)palladium dichloride is particularly preferable as the palladium compound. The amount of the palladium compound to be used is not particularly limited as long as a catalytic amount is used, relative to compound (I-2'') or a salt thereof. It is generally 0.01-1.0 mmole, preferably 0.05-0.2 mmole, per 1 mmole of compound (I-2'') or a salt thereof. As a metal catalyst, a combination of a palladium compound and a copper compound is preferable. When a palladium compound and a copper compound are used in combination, the palladium compound is particularly preferably bis(triphenylphosphine)palladium dichloride and the copper compound is particularly preferably cuprous iodide. The amount of the palladium compound to be used and the amount of the copper compound to be used are not particularly limited as

long as a catalytic amount is used relative to compound (I-2'') or a salt thereof. The amount of the palladium compound to be used is generally 0.01-1.0 mmole, preferably 0.05-0.2 mmole, per 1 mmole of compound (I-2'') or a salt thereof, and the amount of the copper compound to be used is generally 0.01-1.0 mmole, preferably 0.05-0.2 mmole, per 1 mmole of compound (I-2'') or a salt thereof.

In Step C2, an amine compound is preferably used as a base (1), as defined above, and as the amine compound, trialkylamine is preferable. As the trialkylamine, triethylamine and ethyldiisopropylamine are preferable. The amount of the base (1) to be used is generally 1.0-5.0 mmole, preferably 1.0-3.0 mmole, per 1 mmole of compound (I-2'') or a salt thereof.

In Step C2, the amount of the compound (IV) to be used is generally 1.0-2.0 mmole, preferably 1.0-1.3 mmole, per 1 mmole of compound (I-2'') or a salt thereof.

In Step C2, the solvent is not particularly limited as long as the reaction is not adversely affected by the solvent, and, for example, aprotic solvents such as DMF, N,N-dimethylacetamide, DMSO, THF and the like, and the like are mentioned, with preference given to DMF. The amount of the solvent to be used is not particularly limited, and is generally 1-200 mL, preferably 5-20 mL, per 1 mmole of compound (I-2'') or a salt thereof.

In Step C2, the reaction time varies depending on the reagents and solvent to be used, and is generally 2-8 hrs.

In Step C2, the reaction temperature varies depending on the reagents and solvent to be used, and is generally 50°C-150°C, preferably 80°C-100°C.

As the salt of compound (I-2'''), those similar to the salts recited above are mentioned.

Accordingly, the alkynylpurine compound represented by

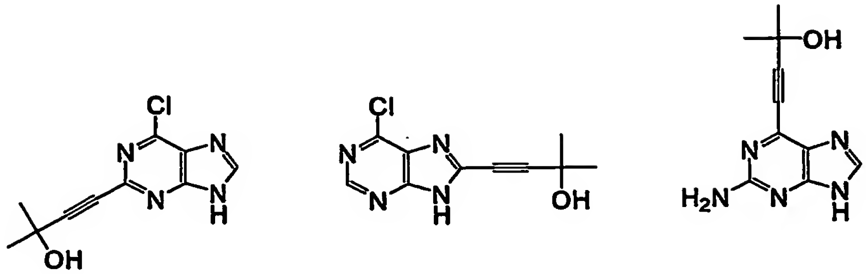
the formula (I-2) is considered to encompass compounds (I-2′), (I-2′′), (I-2′′′)(including isomers such as tautomer and the like, obtainable in each step) and salts thereof obtained by the reactions described in Scheme 2, as well as compounds and salts thereof obtained by the methods according to Scheme 2.

The above-mentioned Steps A1-C1 and A2-C2 may further include steps of protecting a hydroxy group and an amino group with a suitable protecting group as necessary, and removing the protecting group, by a known means for those of ordinary skill in the art of the organic synthesis.

In the above-mentioned Steps A1-C1 and A2-C2, each product may be isolated and/or purified by an isolation or purification means known to those of ordinary skill in the art of the organic synthesis (e.g., crystallization, recrystallization, distillation, chromatography etc.).

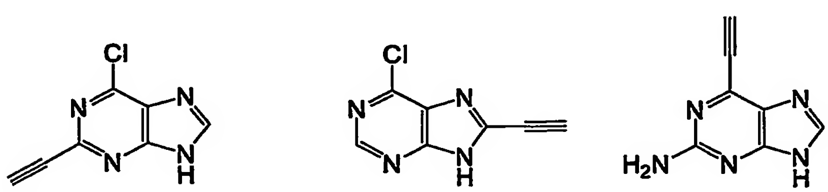
As described above, according to the present invention, an alkynylpurine compound represented by the formula (I) (specifically, compounds of the formula (I-1) and the formula (I-2)) and salts thereof can be produced.

Of the alkynylpurine compounds represented by the formula (I), a compound wherein the alkynyl moiety is $Me_2(OH)C-C\equiv C-$ is preferable as an intermediate for the production of medicaments. The reason therefor is that the alkynyl moiety [$Me_2(OH)C-C\equiv C-$] can be easily converted to ethynyl [$HC\equiv C-$] by a treatment with a base (2) in the above-mentioned Step B1 or B2 (i.e., elimination of acetone via β-elimination). Of the alkynylpurine compounds wherein the alkynyl moiety is $Me_2(OH)C-C\equiv C-$, the following three compounds (having amino-protecting group such as tetrahydropyran-2-yl, benzyl and the like where necessary) are particularly preferable.



In addition, the compound according to the present invention wherein the alkynyl moiety is ethynyl [HC≡C−] can lead many alkynylpurine compounds wherein the alkynyl moiety is A−C≡C− (A is as defined above) by further modification of the ethynyl (see the above-mentioned Step C). A greater number of alkynylpurine derivatives can be also provided by further modification of A, X^1 or X^2, Z^1 or Z^2 of compound (I-1''') or compound (I-2''').

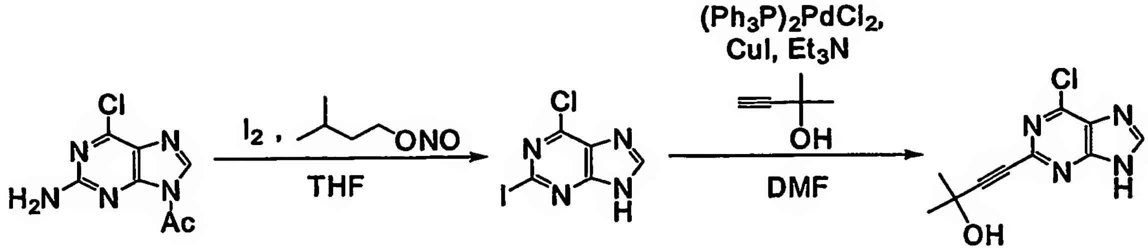
Accordingly, the present invention is characterized in that various alkynylpurine compounds can be derived via an ethynylpurine compound (i.e., compound (I-1) and (I-2) having an alkynyl moiety (R−C≡C−) wherein R is hydrogen atom) as a key intermediate. As the ethynylpurine compound, particularly the following three compounds (having an amino-protecting group, as necessary, such as tetrahydropyran-2-yl, benzyl and the like) are preferable.



The present invention is explained in detail by referring to the following Examples. These Examples are given for exemplification purposes alone and do not limit the present invention in any way.

Example 1

Synthesis of 4-(6-chloropurin-2-yl)-2-methylbutan-3-yn-2-ol



(1) 9-Acetyl-2-amino-6-chloro-9H-purine (10.0 g, 0.047 mole), iodine (9.0 g, 0.036 mole) and isoamyl nitrite (20.0 g, 0.171 mole) were mixed in THF (100 mL) and heated at 50-60°C to allow reaction. After cooling to room temperature, a 15% aqueous sodium thiosulfate solution (100 mL) was added to the obtained reaction mixture and the mixture was extracted three times with methylisobutylketone (50 mL). The obtained organic layers were combined and extracted three times with 5% aqueous sodium hydroxide solution (100 mL). This alkaline aqueous solution was adjusted to pH 4-5 to give yellow crystals. The crystals were collected by filtration and dried under reduced pressure to give 6-chloro-2-iodo-9H-purine (10.0 g, 0.036 mole, yield 76%).

Analytical data

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 8.57 (s, 1H).

^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 116.6, 129.5, 146.3, 147.8, 156.6.

MS (EI) m/z: 282 (M^+, 32), 280 (M^+, 100), 155 (32), 153 (94).

(2) 6-Chloro-2-iodo-9H-purine (2.80 g, 10 mmole), triethylamine (1.21 g, 12 mmole), bis(triphenylphosphine)palladium dichloride (0.30 g, 0.5 mmole), 2-methylbutan-3-yn-2-ol (1.01 g, 12 mmole) and cuprous iodide (0.10 g, 0.5 mmole) were mixed in DMF (20 mL) and the mixture was heated at 90°C for 5 hrs. under a nitrogen atmosphere. DMF was evaporated under reduced pressure and the obtained residue was applied to silica gel column chromatography to give the objective 4-(6-chloro-9H-purin-2-yl)-2-methylbutan-3-yn-2-ol (1.36 g, 5.74 mmole, yield 57%).

Analytical data

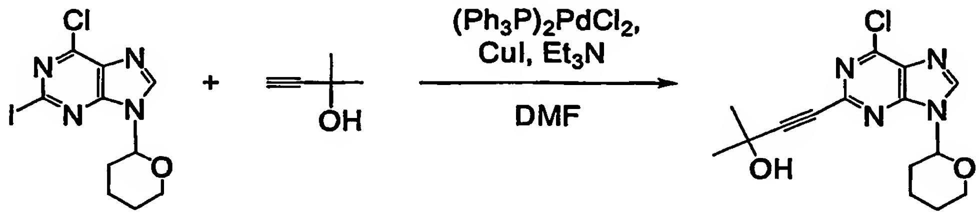
^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 1.48 (s, 6H), 5.68 (br, 1H), 8.70 (s, 1H), 13.93 (br, 1H).

^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 30.9, 63.4, 79.5, 92.8, 129.5, 144.0, 146.6, 148.1, 153.1.

MS (EI) m/z: 238 (M^+, 6.5), 236 (M^+, 17), 223 (28), 221 (100), 195 (20), 193 (61), 181 (12), 179 (34), 143 (27).

Example 2

Synthesis of 4-[6-chloro-9-(tetrahydropyran-2-yl)-9H-purin-2-yl]-2-methylbutan-3-yn-2-ol



6-Chloro-2-iodo-9-(tetrahydropyran-2-yl)-9H-purine (2.80 g, 7.8 mmole), triethylamine (0.96 g, 9.5 mmole), bis(triphenylphosphine)palladium dichloride (0.28 g, 0.40 mmole), 2-methylbutan-3-yn-2-ol (0.83 g, 9.9 mmole) and cuprous iodide (0.10 g, 0.53 mmole) were mixed in DMF (15 mL) and the mixture was heated at 90°C for 5 hrs. under a nitrogen atmosphere. DMF was evaporated under reduced pressure and the obtained reaction mixture was subjected to silica gel column chromatography to give the objective 4-[6-chloro-9-(tetrahydropyran-2-yl)-9H-purin-2-yl]-2-methylbutan-3-yn-2-ol (1.50 g, 4.7 mmole, yield 60%).

Analytical data

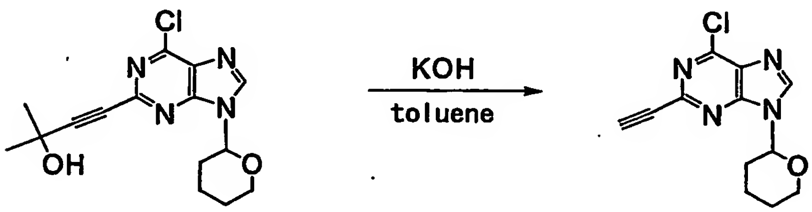
^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 1.53-1.70 (m, 8H), 1.75-1.85 (m, 1H), 1.97-2.11 (m, 2H), 2.25-2.29 (m, 1H), 3.73-3.81 (m, 1H), 4.02-4.07 (m, 1H), 5.72-5.83 (m, 2H), 8.96 (s, 1H).

^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 22.0, 24.4, 29.8, 31.0, 63.4, 67.7, 79.3, 81.4, 93.7, 130.0, 144.2, 146.0, 148.8, 151.1.

MS (EI) m/z: 322 (M^+, 1.2), 320 (M^+, 4.0), 239 (2.0), 237 (11.9), 85 (100).

Example 3

Synthesis of 6-chloro-2-ethynyl-9-(tetrahydropyran-2-yl)-9H-purine



4-[6-Chloro-9-(tetrahydropyran-2-yl)-9H-purin-2-yl]-2-methylbutan-3-yn-2-ol (0.15 g, 0.47 mmole) and potassium hydroxide (0.15 g, 2.6 mmole) were added to toluene (30 mL) and the mixture was heated under reflux for 3 hrs. The reaction mixture was cooled to room temperature and washed with water (30 mL×2). Toluene was evaporated under reduced pressure to give the objective 6-chloro-2-ethynyl-9-(tetrahydropyran-2-yl)-9H-purine (0.10 g, 0.38 mmole, yield 81%).

Analytical data

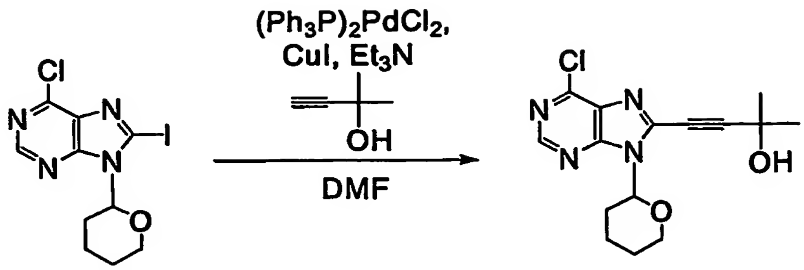
^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 1.60-1.80 (m, 3H), 1.90-2.02 (m, 2H), 2.24-2.29 (m, 1H), 3.72-3.78 (m, 1H), 4.02-4.04 (m, 1H), 4.51 (s, 1H), 5.75-5.79 (m, 1H), 8.86 (s, 1H).

^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 22.1, 24.4, 29.8, 67.7, 78.9, 81.5, 90.1, 130.7, 143.4, 146.5, 148.9, 151.1.

MS (EI) m/z: 264 (M^+, 2.8), 262 (M^+, 8.7), 234 (3.7), 181 (4.1), 179 (19), 85 (100).

Example 4

Synthesis of 4-[6-chloro-9-(tetrahydropyran-2-yl)-9H-purin-8-yl]-2-methylbutan-3-yn-2-ol



6-Chloro-8-iodo-9-(tetrahydropyran-2-yl)-9H-purine (0.8 g, 2.2 mmole) synthesized according to the method described in Synth. Commun., 1998, 28 (23), 4303-4315, 2-methylbutan-3-yn-2-ol (0.28 g, 3.3 mmole), triethylamine (0.30 g, 3.0 mmole), bis(triphenylphosphine)palladium dichloride (0.14 g, 0.20 mmole) and cuprous iodide (0.06 g, 0.32 mmole) were mixed in DMF (100 mL), and the mixture was heated at 80°C for 3 hrs. under a nitrogen atmosphere. DMF was evaporated under reduced pressure and the obtained reaction mixture was added to an aqueous ammonium chloride solution. The mixture was extracted with methylisobutylketone and the organic layer was dried over anhydrous magnesium sulfate. The organic solvent was evaporated, and the obtained residue was separated and purified by silica gel column chromatography to give the objective 4-[6-chloro-9-(tetrahydropyran-2-yl)-9H-purin-8-yl]-2-methylbutan-3-yn-2-ol (0.30 g, 0.94 mmole, yield 43%).

Analytical data

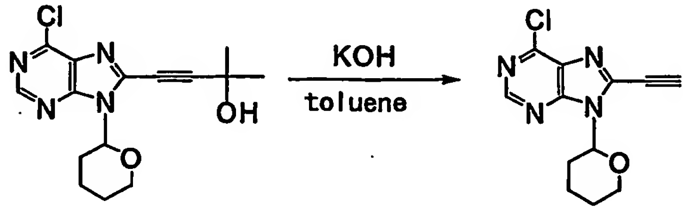
^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 1.60 (s, 6H), 1.60-1.80 (m, 3H), 1.90-2.10 (m, 2H), 2.85-2.95 (m, 1H), 3.70-3.76 (m, 1H), 4.10-4.15 (m, 1H), 5.80-5.85 (m, 1H), 5.99 (br, 1H), 8.84 (s, 1H).

^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 22.6, 24.4, 28.4, 30.6, 63.8, 68.2, 70.2, 83.4, 104.3, 130.3, 138.4, 149.0, 150.9, 152.2.

MS (EI) m/z: 322 (M^+, 1.6), 320 (M^+, 5.2), 239 (5.7), 237 (37), 85 (100).

Example 5

Synthesis of 6-chloro-8-ethynyl-9-(tetrahydropyran-2-yl)-9H-purine



4-[6-Chloro-9-(tetrahydropyran-2-yl)-9H-purin-8-yl]-2-methylbutan-3-yn-2-ol (0.10 g, 0.31 mmole) and potassium hydroxide (0.10 g, 1.78 mmole) were added to toluene (20 mL) and the mixture was heated at 80°C for 3 hrs. The reaction mixture was cooled to room temperature and washed with water (20 mL×2). Toluene was evaporated under reduced pressure and the obtained residue was subjected to column chromatography to give the objective 6-chloro-8-ethynyl-9-(tetrahydropyran-2-yl)-9H-purine (0.06 g, 0.27 mmole, yield 74%).

Analytical data

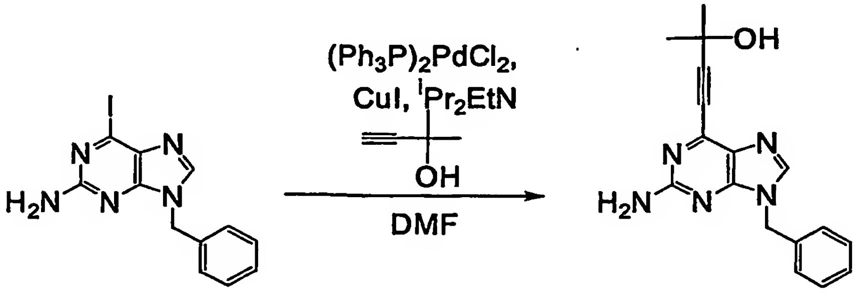
^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 1.60-1.80 (m, 3H), 1.90-2.10 (m, 2H), 2.85-2.90 (m, 1H), 3.67-3.75 (m, 1H), 4.02-4.10 (m, 1H), 5.28 (s, 1H), 5.80-5.85 (m, 1H), 8.86 (s, 1H).

^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 22.4, 24.4, 28.4, 68.2, 72.4, 83.6, 90.1, 130.3, 137.7, 149.5, 150.9, 152.6.

MS (EI) m/z: 264 (M^+, 2.3), 262 (M^+, 5.4), 181 (6.8), 179 (19), 85 (100).

Example 6

Synthesis of 4-(2-amino-9-benzyl-9H-purin-6-yl)-2-methylbutan-3-yn-2-ol



2-Amino-9-benzyl-6-iodo-9H-purine (1.8 g, 5.1 mmole), 2-

methylbutan-3-yn-2-ol (0.50 g, 5.9 mmole), ethyldiisopropylamine (0.78 g, 6.0 mmole), bis(triphenylphosphine)palladium dichloride (0.18 g, 0.26 mmole) and cuprous iodide (0.048 g, 0.25 mmole) were mixed in DMF (20 mL), and the mixture was heated at 80°C for 3 hrs. under a nitrogen atmosphere. After cooling to room temperature, a saturated aqueous ammonium chloride solution (50 mL) was added to the mixture and the mixture was extracted with methylisobutylketone (50 mL×3). The organic layer was dried over anhydrous magnesium sulfate. The organic solvent was evaporated, and the obtained residue was separated and purified by silica gel column chromatography to give the objective 4-(2-amino-9-benzyl-9H-purin-6-yl)-2-methylbutan-3-yn-2-ol (1.0 g, 3.3 mmole, yield 66%).

Analytical data

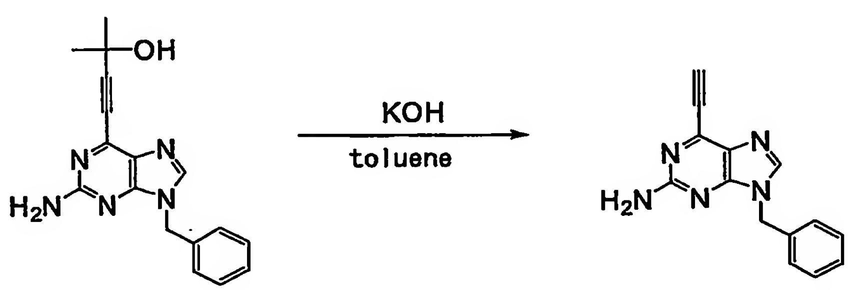
^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 1.48 (s, 6H), 5.28 (s, 2H), 5.68 (s, 1H), 6.60 (br s, 2H), 7.22-7.34 (m, 5H), 8.19 (s, 1H).

^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 31.18, 45.67, 63.63, 76.52, 101.40, 126.95, 127.52, 128.54, 136.68, 140.97, 142.97, 153.42, 160.23.

MS (EI) m/z: 307 (M^+).

Example 7

Synthesis of 2-amino-9-benzyl-6-ethynyl-9H-purine



4-(2-Amino-9-benzyl-9H-purin-6-yl)-2-methylbutan-3-yn-2-ol (50.0 mg, 0.148 mmole) and potassium hydroxide (50 mg, 0.89 mmole) were added to toluene (10 mL) and the mixture was

heated under reflux for 5 hrs. The reaction mixture was cooled to room temperature and washed with water (10 mL×2). Toluene was evaporated under reduced pressure to give the objective product, 2-amino-9-benzyl-6-ethynyl-9H-purine (34.0 mg, 0.136 mmole, yield 92%).

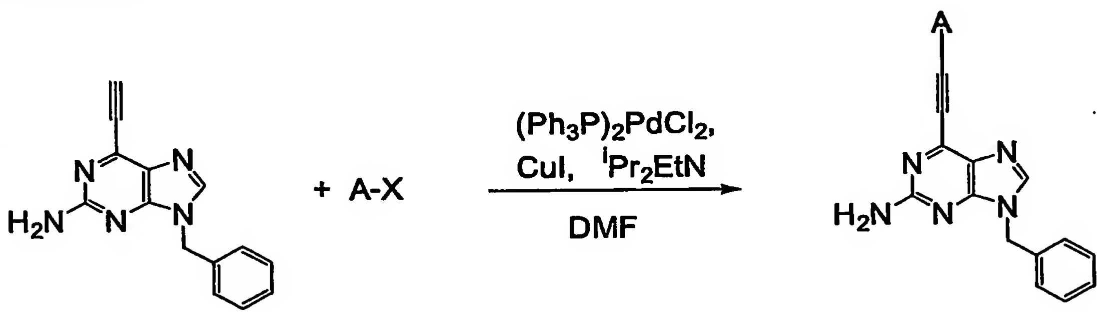
Analytical data

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 4.22 (s, 1H), 5.30 (s, 2H), 6.33 (br, 2H), 7.24-7.34 (m, 5H), 7.37 (dd, 1H), 8.05 (s, 1H).

^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 45.7, 78.4, 84.9, 126.8, 127.3, 127.8, 128.2, 135.9, 140.1, 142.6, 153.3, 159.9.

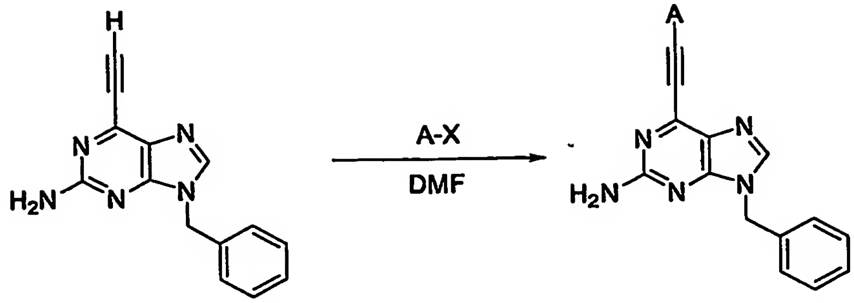
MS (EI, 70 eV) m/z: 249 (M^+, 24), 91 (100).

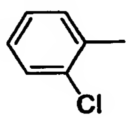
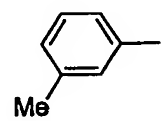
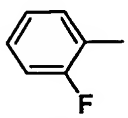
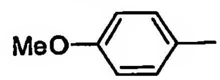
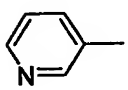
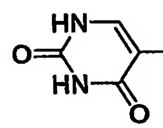
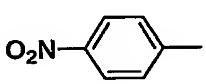
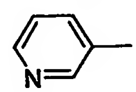
Example 8



Halide: A-X (0.39 mmole), bis(triphenylphosphine)palladium dichloride (13 mg, 0.018 mmole), ethyldiisopropylamine (0.19 g, 1.08 mmole) and cuprous iodide (3.4 mg, 0.018 mmole) were added to DMF (3 mL). Thereto was added a solution (2 mL) of 2-amino-9-benzyl-6-ethynyl-9H-purine (100 mg, 0.36 mmole) in DMF under a nitrogen atmosphere. The obtained reaction mixture was heated at 80°C (see the following Table 1 for reaction time (Time (h))). The organic solvent was evaporated under reduced pressure and the residue was dissolved in THF (5 mL). The solution was washed with aqueous ammonia and THF was evaporated under reduced pressure. The residue was purified by silica gel chromatography to give the corresponding 2-amino-9-benzyl-6-(substituted ethynyl)-9H-purine (see the following Table 1 for Yield (%)).

Table 1



A	X	Time (h)	Yield (%)	A	X	Time (h)	Yield (%)
	I	8	58		I	8	45
	I	8	63		I	8	71
	I	8	65		I	8	34
	I	8	91		Br	8	30

2-Amino-9-benzyl-6-(2-chlorophenylethynyl)-9H-purine

Analytical data

^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 5.21 (s, 2H), 5.29 (br, 2H), 7.17-7.32 (m, 7H), 7.37 (dd, 1H), 7.65 (dd, 1H), 7.76 (s, 1H).

^{13}C-NMR (125 MHz, $CDCl_3$) δ (ppm): 45.8, 87.2, 92.8, 120.6, 125.5, 126.7, 127.5, 127.9, 128.1, 128.4, 129.7, 133.3, 134.2, 135.8, 140.3, 142.2, 153.0, 158.6.

MS (EI, 70 eV) m/z: 361 (M^+, 2), 359 (M^+, 7), 277 (81), 183 (45), 91 (100).

2-Amino-9-benzyl-6-(2-fluorophenylethynyl)-9H-purine

Analytical data

^{1}H-NMR (500 MHz, DMSO-d_6) δ (ppm): 5.25 (s, 2H), 6.67 (br, 2H), 7.16-7.35 (m, 7H), 7.50 (dd, 1H), 7.64 (s, 1H), 8.28 (s, 1H).

^{13}C-NMR (125 MHz, DMSO-d_6) δ (ppm): 45.3, 86.8, 89.2, 108.8,

108.9, 115.4, 115.5, 124.5, 126.6, 127.2, 128.2, 132.0, 133.4, 136.2, 139.7, 160.0, 160.7, 162.7.
MS (EI, 70 eV) m/z: 343 (M^+, 23), 91 (100), 57 (36).

2-Amino-9-benzyl-6-(pyridin-3-ylethynyl)-9H-purine
Analytical data
^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 5.23 (s, 2H), 5.41 (br, 2H), 7.19-7.23 (m, 2H), 7.28-7.35 (m, 4H), 7.78 (s, 1H), 7.97 (d, 1H), 8.58 (d, 1H), 8.88 (s, 1H).
^{13}C-NMR (125 MHz, $CDCl_3$) δ (ppm): 46.0, 84.2, 85.0, 122.1, 126.7, 127.7, 128.2, 128.4, 138.7, 142.8, 149.0, 152.0, 157.9.

2-Amino-9-benzyl-6-(4-nitrophenylethynyl)-9H-purine
Analytical data
^{1}H-NMR (500 MHz, DMSO-d_6) δ (ppm): 5.32 (s, 2H), 7.22-7.32 (m, 5H), 7.85 (s, 1H), 8.09 (d, 2H), 8.28 (s, 2H), 8.77 (s, 1H).
^{13}C-NMR (125 MHz, DMSO-d_6) δ (ppm): 47.4, 121.6, 123.6, 124.9, 128.4, 128.9, 129.3, 129.7, 136.6, 138.8, 143.1, 149.2, 158.7.
MS (EI, 70 eV) m/z: 339 (7), 277 (14), 149 (100), 57 (48).

2-Amino-9-benzyl-6-(3-methylphenylethynyl)-9H-purine
Analytical data
^{1}H-NMR (250 MHz, $CDCl_3$) δ (ppm): 2.35 (s, 3H), 5.24 (s, 2H), 5.98 (br, 2H), 7.24-7.35 (m, 7H), 7.53 (d, 1H), 7.58 (s, 1H), 7.86 (s, 1H).
^{13}C-NMR (62.5 MHz, $CDCl_3$) δ (ppm): 21.0, 46.9, 83.3, 99.5, 121.0, 127.7, 128.3, 128.5, 129.1, 129.9, 130.9, 133.3, 134.9, 138.1, 140.8, 143.1, 145.5, 154.1, 159.8.
MS (EI, 70 eV) m/z: 339 (M^+, 14), 277 (24), 149 (100), 91 (49), 57 (48).

2-Amino-9-benzyl-6-(4-methoxyphenylethynyl)-9H-purine
Analytical data

^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 3.75 (s, 3H), 5.18 (s, 2H), 5.41 (br, 2H), 6.81 (d, 2H), 7.15-7.29 (m, 5H), 7.59 (d, 2H), 7.72 (s, 1H).
^{13}C-NMR (125 MHz, $CDCl_3$) δ (ppm): 45.8, 54.3, 82.1, 97.4, 113.1, 126.6, 127.4, 128.1, 131.0, 133.5, 134.3, 141.3, 141.6, 152.6, 158.8, 159.9.
MS (EI, 70 eV) m/z: 355 (M^+, 10), 281 (34), 277 (19), 147 (43), 57 (100).

5-[(2-Amino-9-benzyl-9H-purin-6-yl)ethynyl]-1H-pyrimidine-2,4-dion
Analytical data
^{1}H-NMR (250 MHz, DMSO-d_6) δ (ppm): 5.29 (s, 2H), 6.72 (br, 2H), 7.25-7.31 (m, 5H), 8.03 (s, 1H), 8.21 (s, 1H), 11.74 (br, 2H).
^{13}C-NMR (62.5 MHz, DMSO-d_6) δ (ppm): 47.4, 85.4, 100.4, 113.4, 117.8, 119.0, 127.1, 128.7, 134.7, 137.2, 147.0, 155.6, 159.1, 163.9, 172.5, 174.0.

Industrial Applicability

According to the present invention, a method for producing an alkynylpurine compound and a salt thereof useful as an intermediate for medicament production safely, conveniently and economically from the corresponding purine compound and a salt thereof, as well as an alkynylpurine compound and a salt thereof useful as an intermediate for medicament production can be provided.

This application is based on a patent application No. 2002-175015 filed in Japan, the contents of which are hereby incorporated by reference.